Executive Function and Attention Profiles of Children with ADHD and / or Reading Disorder: Developmental Neuropsychology and Genetic Contributions

Student: Gian Marco Marzocchi

Supervisor: Prof. Tim Shallice

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Chapter 1

Frontal lobe processes and their development

1.1 Neuroanatomy of Executive Function

Executive functions are high-level cognitive functions that are involved in the control and direction of lower-level functions. For the purposes of consistency with prior literature, I use the terms "frontal" and "executive" interchangeably when referring to broad classifications of tests, but it will be clear that I adopt a much more specific approach when trying to understand and explain the true functional localization of these processes. One very general method of separating the different facets of frontal lobe functioning is based on a fundamental neuroanatomical distinction (see Figure 1.1).

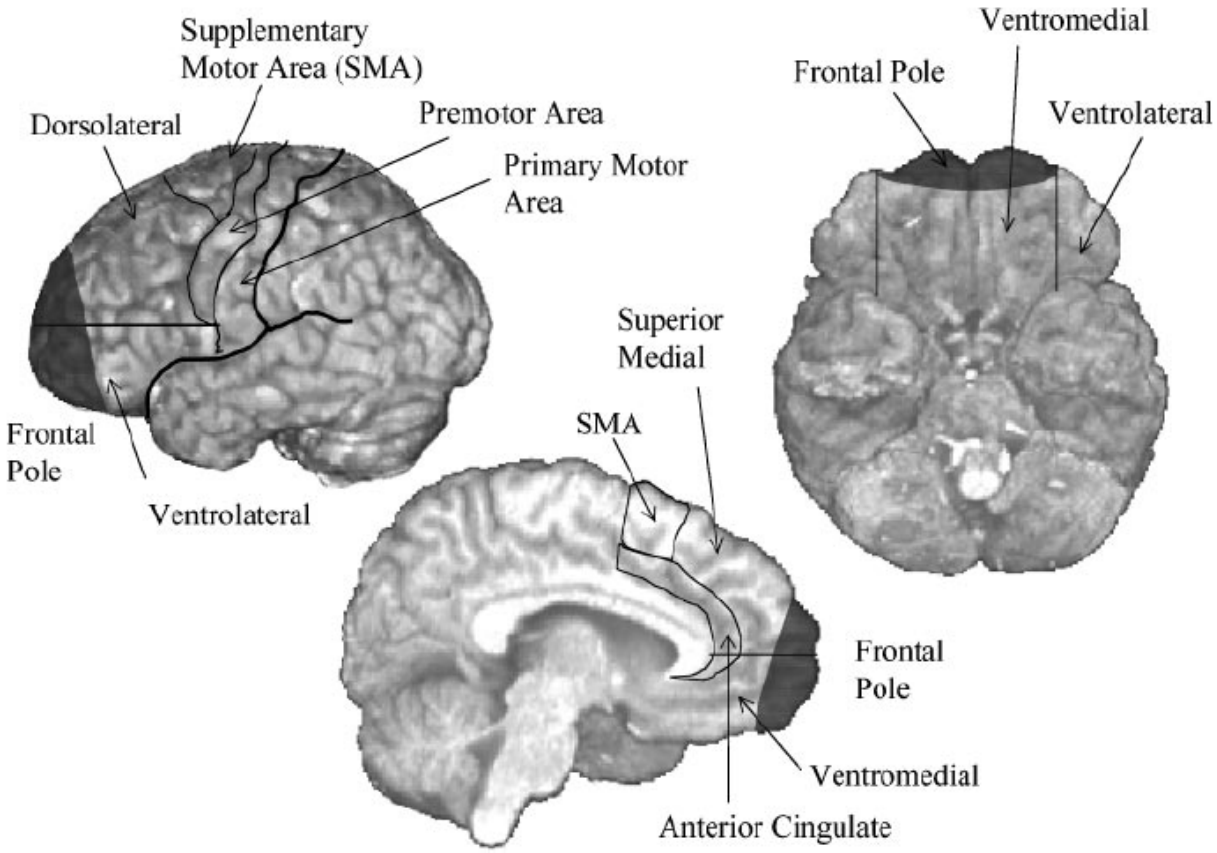


Figure 1.1 The major functional subdivisions of the human frontal lobes.

The brain areas anterior to the central sulcus, approximately one-third of the cerebral cortex, comprise the frontal lobes. Frontal cortex can be divided into three principal regions: the precentral or primary motor cortex, the prefrontal cortex, and the limbic cortex. The prefrontal cortex refers to the most anterior regions of the frontal lobes. Traditionally, the prefrontal cortex is divided into the following anatomical regions: the medial frontal cortex (Brodmann's area 24, anterior cingulate cortex), the Ventral Prefrontal cortex VPFC (Brodmann's areas 11 and 12), and the Dorsolateral prefrontal cortex DLPFC (Brodmann's areas 9, 10, 46).

The prefrontal cortex, along with its underlying subcortical regions, is extensively interconnected with the major sensory and motor systems of the brain. Connections from posterior cortical areas, particularly areas of multimodal convergence, bring information about the external environment. Subcortical pathways bring details about internal states. These interconnections between prefrontal cortex and other cortical and subcortical brain regions have been mapped out in great detail in nonhuman primates (see Cummings (1993), Damasio and Anderson (1993), Mega and Cummings (1994) for reviews). Cummings (1993) and Mega and Cummings (1994) provided comprehensive reviews of five neuroanatomical circuits connecting regions of the frontal lobes with subcortical structures, such as the striatum, globus pallidus, and thalamus. The following is a synthesis of the material contained in the above-mentioned sources. Two of the frontal–subcortical circuits are involved in the control of motor function and eye movements, whereas the remaining three circuits are concerned with nonmotoric behavior. Originating in the frontal lobes, the five circuits share the same basic structure. The first pathway, composed of excitatory glutaminergic fibers, projects from the frontal lobes to a discrete region in the striatum. From the striatum, inhibitory GABA fibers connect directly to the globus pallidus and substantia nigra, which in turn send inhibitory GABA fibers to specific thalamic nuclei. In addition, there are indirect projections from the striatum to the external globus pallidus. From there, inhibitory GABA projections lead to the subthalamic nucleus; then, excitatory glutaminergic fibers project back to the internal globus

pallidus and substantia nigra. Finally, there are direct excitatory connections from the thalamus back to the frontal lobes, completing the semi-closed circuits. The circuits are anatomically separate, with each circuit emanating from and projecting to a discrete region of each member component. Figure 1.2 summarizes the basic structure of frontal–subcortical circuits. Three of the five frontal–subcortical circuits are involved in cognition, emotion, and motivation and are therefore most relevant to the current review. The frontal lobe are grossly divided into cognitive (DLPFC) and affective (VPFC) functions.

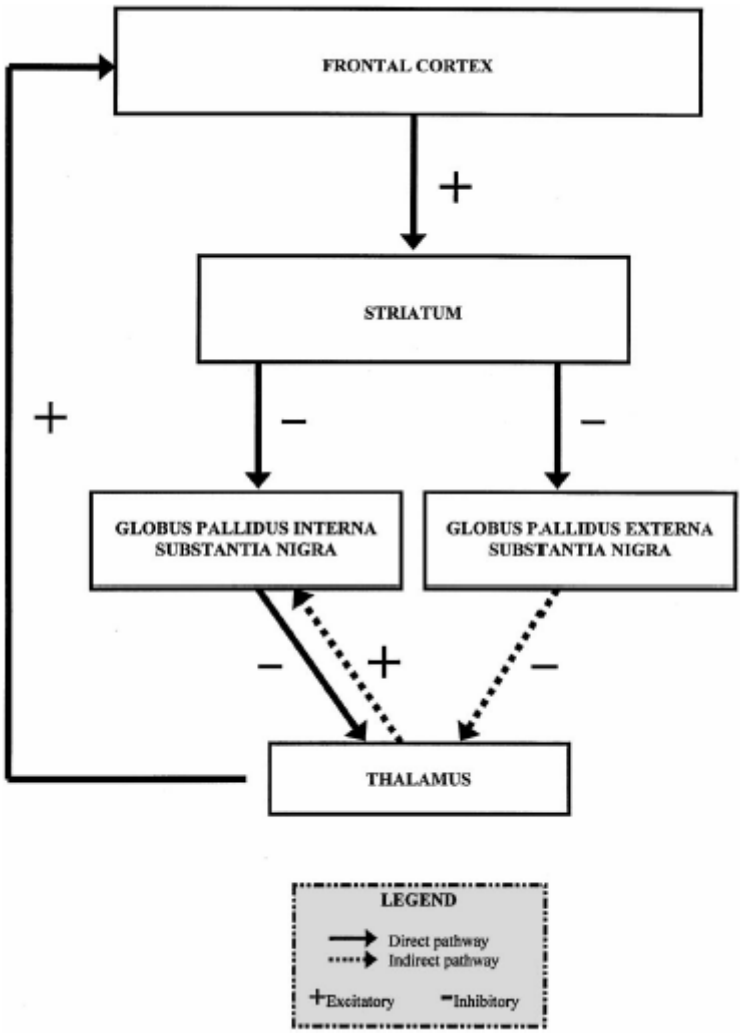


Figure 1.2. A schematic representation of the basic structure of frontal-subcortical circuits (adapted from Cummings, 1993).

The *dorsolateral prefrontal circuit* begins in Brodmann's areas 9 and 10 of the lateral, anterior frontal lobe, which are frontal association areas. The DLPFC is part of the archicortical trend originating in the hippocampus. A projection from the frontal lobes leads to the dorsolateral caudate nucleus, which sends fibers to specific regions of the globus pallidus and substantia nigra. These areas are, in turn, connected to the ventral anterior and medial dorsal thalamic nuclei. Each of the dorsolateral circuit's component regions has open, reciprocal connections with functionally related frontal and subcortical structures, allowing for the synthesis of information from various regions of the brain. According to Cummings (1993), dysfunction in the dorsolateral prefrontal circuit is associated with circuit-specific problems: decreased fluency, perseveration, difficulty shifting set, poor recall/retrieval of information, reduced mental control, limited abstraction ability, and poor response inhibition. These cognitive processes form the basis of what is referred to as executive functioning (Goldman-Rakic 1987, Milner 1963). Patients with lesions restricted to this region typically demonstrate intact perception, calculation, language ability, and storage of memories. It is involved in spatial and conceptual reasoning processes.

The Ventral Prefrontal Cortex (VPFC) is part of the paleocortical trend emerging from the caudal orbitofrontal (olfactory) cortex. The *VPFC – subcortical circuit* originates in the orbitofrontal cortex, projecting to the ventral caudate nucleus, the globus pallidus and substantia nigra, and the ventral anterior and medial dorsal thalamic nuclei. Moreover, the ventral frontal cortex has open interconnections with the dorsolateral prefrontal cortex, the temporal pole, and the amygdala. The VPFC is intimately connected with limbic nuclei involved in emotional processing (Nauta 1971, Pandya & Barnes, 1987), including the acquisition and reversal of stimulus-reward associations (Mishkin, 1964 ; Rolls, 2000). The involvement of the ventral medial/orbitofrontal region in inhibition, emotion, and reward processing suggests a role in behavioral self-regulation, as shown in numerous case studies of patients with pathology in this area (Eslinger & Damasio 1985). Lesions specific to the circuit may result in disinhibition and impulsivity (Cummings, 1993). Obsessive-compulsive disorder may also result from dysfunction in the ventral frontal – subcortical

circuit. In spite of the obvious importance of these processes to human behavior, they are not adequately assessed by standard neuropsychological assessment. The ventral frontal – subcortical circuit is said to underlie social behavior.

The *medial– frontal* circuit arises in the anterior cingulate cortex. It contains the nucleus accumbens, also called the ventromedial striatum, the globus pallidus and substantia nigra, and the medial dorsal thalamic nucleus. The anterior cingulate has interconnections with dorsolateral prefrontal cortex and the amygdala; it also receives input from the ventral tegmental area. The medial frontal–subcortical circuit is involved in motivation. Lesions specific to this circuit may produce apathy, lack of motivation, decreased interest in and engagement with the environment, and poor behavioral maintenance.

The frontal poles, particularly on the right, are involved in more recently evolved aspects of human nature: autonoetic consciousness and self-awareness. The importance of polar regions in specific higher human functions has also been highlighted in studies of humor and theory of mind (Baron-Cohen et al. 1994; Shammi & Stuss 1999; Stuss et al. 2001). We therefore consider the frontal polar region to be distinctly involved in processes that define us as human.

In summary, the frontal–subcortical circuits are extensively connected to each other at the level of the frontal lobes. The circuits are discrete in subcortical regions. The dorsolateral circuit, because of its neuroanatomy, is uniquely able to integrate information from all three frontal–subcortical circuits. Here information from the external world joins cognitive and emotional states of the individual. The integrated input can then be used in the production of executive, motor, and oculomotor behavior.

This chapter reviews language, memory and attentional functions which are neuroanatomically controlled by frontal lobes since there are tasks related to these cognitive processes.

1.2 Language processes

Excluding motor deficits (e.g., articulation problems), and Broca's aphasia, the language deficits related to the frontal lobes can be grouped globally under activation and formulation (paralinguistic) deficits (Alexander et al. 1989). Activation problems in speech output ("dynamic aphasia") are associated with medial frontal damage (anterior cingulate gyrus and supplementary motor area). Activation deficits can be tested by requiring the patient to generate a list of words beginning with a specific letter (phonological or letter fluency) or from a specific semantic category (semantic or category fluency). Next to the Wisconsin Card Sorting Test (WCST, see below), letter-based fluency is the most popular frontal test; its face validity derives from its lack of specification by external cues. It is traditionally considered to reflect left frontal function (Milner, 1964, Perret 1974), although other areas of damage have been shown to produce impairment on this task (see Stuss et al. 1998 for review). In Stuss et al (1998) study on 74 focal lesion patients (Stuss et al. 1998), the left DLPFC patients were indeed the most impaired. Right DLPFC and VPFC patients were not impaired. However, patients with left parietal damage were also impaired and in fact could not be distinguished from the left DLPFC patients. Consistent with the role of superior medial regions in activation, superior medial damage on either side was also associated with impaired letter-based fluency. This left DLPFC, parietal, and superior medial frontal regional pattern is activated in functional neuroimaging studies involving word generation (Cabeza & Nyberg 2000). Posterior superolateral temporal regions are also implicated (Wise et al. 1991). Semantic fluency was impaired in all patient groups except for right posterior. Further differentiation of frontal and temporal effects can be derived from process analysis of the size of semantically related clusters of words generated on semantic fluency (related to left temporal lesions) and switching between clusters on either letter-based or semantic fluency, related to left DLPFC or superior medial frontal lesions (Troyer et al. 1998). The formulation problems, or disorders of discourse, are generative and narrative in nature. They reflect problems in planning and goal attainment. At the level of sentence generation and spontaneous utilization of complex syntax, deficits have only been described with

left-sided lesions. At the level of story narrative, lesions in left dorsolateral and prefrontal regions may produce impairments. Left-sided lesions result in simplification and repetition (perseveration) of sentence forms, and omissions of elements. Right-sided lesions cause amplification of details, wandering from the topic and insertion of irrelevant elements, and dysprosody, all leading to loss of narrative coherence (Joanette et al. 1990).

1.3 Memory functioning

In considering the role of the frontal lobes in memory, it is useful to distinguish between basic associative processes of cue-engram interaction (mediated by medial temporal lobe/hippocampal structures), and strategic processes involved in the coordination, elaboration, and interpretation of these associations (mediated by the frontal lobes) (Luria 1973, Moscovitch 1992). The role of the frontal lobes on memory tasks is one of control and direction, hence the phrase "working with memory" (Moscovitch,1992). Damage to the frontal lobes (other than extension to basal forebrain areas) does not result in clinically diagnosed amnesia. Given traditional neuropsychology's strength in assessing medial temporal lobe amnesic syndromes, early clinical memory tests were more suited to the measure of associative than strategic processes. This imbalance has persisted. Whereas current clinical neuropsychological memory tests such as the Wechsler Memory Scale (Wechsler, 1997) tap both associative and strategic processes, few attempts have been made to quantify these skills separately, causing the clinical neuropsychologist to resort to qualitative analysis in the interpretation of frontal lesion effects on memory. A major development in this respect is the California Verbal Learning Test (Delis et al. 1987). This test includes measures of serial position learning, semantic organization, interference effects, cued recall, recognition, and response bias. Although similar measures are incorporated into the latest Wechsler Memory Scale revision (Wechsler 1997), the verbal learning test in this battery contains semantically unrelated words, precluding analysis of semantic clustering. The effects of frontal brain damage on these and other measures were studied by Stuss and colleagues (1994), who

showed that subjective organization (pair frequency), was specifically affected by frontal damage, although the intrafrontal lesion location was not a factor. Right DLPFC patients had increased intralist repetitions, possibly owing to a monitoring deficit. Category clustering deficits were not found, although these have been reported elsewhere (Gershberg & Shimamura 1995). Recognition was also affected by frontal damage. Analysis of this effect revealed that it was related to subtle anomia in left DLPFC patients and subtle associative mnemonic deficits in patients with medial frontal damage extending to septal regions. A subsequent meta-analysis confirmed a small but significant role for the frontal lobes in recognition memory (Wheeler et al. 1995), but only on tests that had an organizational component such as categorized lists. Focal lesion studies have demonstrated the importance of the frontal lobes on retrieval tasks in which monitoring, verification, and placement of information in temporal and spatial contexts are of critical importance (Milner et al. 1985, Stuss et al. 1994). In the past decade, the role of the frontal lobes in memory has been greatly elaborated by functional neuroimaging studies (Cabeza & Nyberg 2000), which allow for separation of mnemonic processes not possible in straight behavioral research.

Fletchter, et al., 1998a; 1998b studied the role of prefrontal cortex involved in episodic memory tasks (learning of list of words), separating the encoding and the retrieval operations. As far as the encoding phase is concerned, PET activity was maximum in left prefrontal cortex, in particular in the dorsolateral area when the lists of words were not organized. The activation of the ventral and anterior regions of the prefrontal cortex were not maximally activated during the organization of the items and this could mean a less specific involvement of the ventral and anterior areas in the encoding phase of an episodic memory task.

Of particular importance is the role of the right frontal lobe in episodic memory retrieval (Tulving et al. 1994), which is consistent with the right lateralization often observed in neuropsychological patients with paramnestic disorders. Imaging work has provided greater intrafrontal specificity in relation to retrieval success, retrieval monitoring, contextual recall, and material specificity (Cabeza & Nyberg 2000). In addition to the right hemispheric bias in retrieval,

retrieval operations can also be distinguished according to relative DLPFC/VPFC involvement within the right hemisphere. VPFC is involved in retrieval cue specification, whereas DLPFC is involved in higher-level post-retrieval monitoring operations (Fletcher et al. 1998, Petrides, 1995). This finding provided greater precision to the earlier patient work (Milner et al. 1991, Stuss et al. 1994) and later case studies (Schacter et al. 1996) on the nature and localization of right frontal executive control in memory retrieval. Working memory is historically central to research on frontal lobe function (Fuster 1985, Goldman-Rakic 1987), beginning with the observation that monkeys with frontal lobe damage are deficient in making stimulus-guided responses after the stimulus is removed from view (Jacobsen 1936). After 70 years of research, however, the precise role of the frontal lobes in working memory tasks is still a matter of debate. Much of this debate is concerned with separation of working memory processes such as encoding strategies, storage/maintenance, rehearsal, interference control, inhibition, and scanning of working memory buffers (D'Esposito et al. 2000). These processes are addressed in experimental lesion or event-related functional neuroimaging research on working memory and attentional control. For the purposes of clinical neuropsychological assessment, the important principles follow on those described for long-term memory above. As in long term memory, the frontal lobes' primary role in working memory is in control and manipulation of information held on-line, hence Baddeley's notion of the "central executive" (Baddeley 1986). Whereas the frontal lobes are certainly involved in simple storage and maintenance, these operations are primarily mediated by posterior regions, such as the inferior parietal lobule ("slave systems") (Baddeley 1986, D'Esposito et al. 1995); frontal involvement increases as information held on-line is threatened by interference or exceeds working memory capacity (D'Esposito et al. 2000). The dorsolateral prefrontal cortex (DLPFC) appears to be preferentially involved in monitoring and manipulation (Owen et al. 1996). The role of the ventral prefrontal cortex (VPFC) is less clear, with hypotheses including maintenance, interference control, and inhibition (D'Esposito et al. 2000). Working memory is important to many neuropsychological tests, but few widely used tasks seek to directly assess working memory per se. Digit span or spatial

span tasks are important for determining working memory storage capacity, but do not provide information relating to rehearsal or executive control. Consistent with the neuroimaging evidence described above, a meta-analysis showed no evidence for an effect of frontal lobe lesions on digit or spatial span (D'Esposito & Postle 1999). Reversal of the sequences (e.g., digits backwards) does measure manipulation of information held on-line. Scoring methods that combine forward and backward span confound these capacity and manipulation measures. The latest updates of the Wechsler Instruments have added new tasks stressing manipulation and control (Wechsler 1997a,b) and even allow for a separate "working memory" composite score. This too combines the dissociable processes into a single measure, although the neuropsychologist is still able to examine the more demanding strategic subtests separately. The Brown-Peterson technique taps working memory control processes in the presence of interference (Stuss et al. 1982), and supraspan tests can be used to measure processing when working memory capacity is exceeded (Lezak 1995).

1.4 Anterior Attention Functions

The frontal lobes mediate attentional control in the top-down guidance and direction of other processes. Proper assessment of attentional deficits requires differentiation among distinct attentional processes that can be selectively impaired. Standard assessment is concerned with attentional switching, selective attention, and sustained attention, whereas modern assessment more finely fractionates anterior attentional systems.

From a neuropsychological point of view, many researches showed that frontal brain regions play a significant role in supporting two executive aspects of memory: organizational strategy use in long term memory (Gershberg & Shimamura, 1995; Incisa della Rocchetta & Milner, 1993; Moscovitch, 1992; Stuss et al., 1994) and manipulation of information in working memory (Casey et al., 1995; Jonides et al., 1993; Luciana & Nelson, 1998). In terms of long-term memory, Moscovitch (1992) suggested a model in which posterior brain regions subserve simple associative processing and long-term storage. Frontal brain regions, however, mediate strategic control

processes that facilitate the efficient organization of complex information, which in turn facilitate the formation of robust memory traces (Moscovitch, 1992; Moscovitch & Umiltà, 1990, 1991). This model has been supported by neuroimaging findings of frontal cortex involvement in long-term encoding and retrieval (Nyberg, Caeza, & Tulving, 1996; Petrides, 1995). Posterior brain regions also are thought to subserve the simple maintenance of information in working memory, whereas frontal brain regions appear to mediate the strategic manipulation of information (for an overview, see Petrides, 1995).

1.4.1 Attentional switching

In her classic 1963 study, Milner documented a specific effect of frontal cortical lesions on the Wisconsin Card Sorting Test (WCST). In this test the patient must determine the established sorting criterion (color, form, or number) through a process of trial and error, then shift to a new criterion according to a change in examiner feedback. The WCST has since become the most widely used behavioral measure of frontal lobe function (Heaton et al. 1993). However, posterior damage can affect WCST performance (Anderson et al. 1991). In addition, functional neuroimaging studies indicate frontal and posterior activation in association with WCST performance (Berman et al. 1995). The WCST has been embedded in a larger context of problem-solving by Dias and colleagues (1997). In this framework WCST shifts are regarded as extra-dimensional (across perceptual dimensions, such as from color to form, on the basis of feedback) as opposed intradimensional (shifting within a dimension, such as from red to blue). Extra-dimensional shifting is specifically affected by dorsolateral prefrontal damage in monkeys (Dias et al. 1996) and humans (Owen et al. 1993) and is associated with DLPFC activity in healthy adults (Rogers et al. 2000). This brain-behavior association is consistent with the original development work on the WCST involving patients with DLPFC damage. Stuss et al (2000) directly assessed this DLPFC/VPFC dissociation using the WCST in a large sample of patients with focal lesions. Consistent with the

monkey data, which indicated that VPFC damage does not affect extra-dimensional shifting, patients with DLPFC lesions were impaired, whereas VPFC patients were not impaired. As noted in earlier work (Stuss et al. 1983), the VPFC patients were prone to loss of set, possibly owing to susceptibility to interference. Set loss was also observed in right DLPFC patients, related to poor sustained attention. In summary, the classification and use of the WCST as a frontal measure is justified, but with a number of caveats. Within the frontal lobes, the DLPFC is preferentially involved in the set-shifting aspect of the task. Patients with VPFC damage are relatively intact on this key aspect of the WCST, but they are prone to the less frequently reported set loss errors. As with any test, similar errors can occur for different reasons, such as comprehension deficits. Modern neuropsychological approaches to assessing task switching and other functions of sorting tests include the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Robbins et al. 1994), which includes human analogues of the set-shifting paradigms described in the Dias et al. (1996, 1997) studies, and the California Card Sorting Test (CCST) (Delis et al. 1992). The latter presents a wider variety of verbal and visual sorting criteria (see also Levine et al. 1995b). The CCST incorporates standardized manipulations of environmental support, including identification of groupings executed by the examiner and generation of groupings according to cues. Similar cues can be applied in the WCST to investigate the extent to which deficits are due to self-initiated processes as opposed to a more basic deficit affecting perception or detection of the correct sorting criterion (Stuss et al. 2000). This information may be used to generate rehabilitation hypotheses.

1.4.2 Selective Attention

Deficient selective attention results in omitted responses to important stimuli or enhanced reactivity to irrelevant information. The Stroop test (Stroop 1935) includes a key demand on selective attention of a given response characteristic (i.e., color naming) to the exclusion of a more dominant one (i.e., word reading). The Stroop interference effect is among the most extensively studied phenomena in experimental psychology (MacLeod 1991), although the experimental work has had

no discernable effect on clinical versions of the test. Lesion studies have emphasized right or left DLPFC effects on this measure (Perret 1974, Stuss et al. 1981, Vendrell et al. 1995), whereas functional neuroimaging studies have emphasized the role of medial frontal (in particular anterior cingulate) regions in performance on the Stroop interference condition (Bench et al. 1993, Pardo et al. 1990). In a large sample of focal lesion patients, Stuss et al (2001b) found that the deficit associated with left DLPFC damage could be accounted for by impaired color naming (rather than interference). Patients with frontal damage were slowed on all three conditions. Patients with superior medial lesions (especially on the right) committed the most errors, corresponding to this region's role in maintaining the strength of an activated (selected) intention (Devinsky et al. 1995, Goldberg 1985). Inferior medial patients performed normally. The inconsistency with prior lesion research could be explained by the fact that the prior studies did not correct performance in the interference condition for slowing in the color naming condition.

1.4.3 Sustained Attention

There is a surprising lack of widely accepted measures for sustained attention (detection of targets over a prolonged time period) in traditional clinical neuropsychology. Whereas letter cancellation or other "vigilance" tasks are used (Lezak 1995), there are few data relating performance on these paper-and pencil measures to frontal function. Continuous performance tests are sensitive to right frontal pathology, especially when the target complexity is increased (i.e., respond to "O" following "X"), as opposed to simple vigilance tasks (Reuckert & Grafman 1996,Wilkins et al. 1987) and are associated with right frontal activation in healthy adults (Deutsch et al. 1987, Pardo et al. 1991). Several investigators have highlighted the importance of dull, repetitive tasks in tapping top-down modulation of endogenous arousal (Robertson et al. 1997). Accordingly, slow sustained attention tasks are more sensitive to right frontal pathology than fast-paced ones (Reuckert & Grafman 1998, Wilkins et al. 1987). The Sustained Attention to Response Task (SART; Robertson et al. 1997) and

the Elevator Counting Test (Robertson et al. 1991) are modern neuropsychological tests of these sustained attention abilities stressing maintenance of endogenous arousal.

1.5 Strategy Application

"We had many systems failures and they were in need of your constant attention. Many days I'd start an experiment in the morning to get it running and then I'd run over and help hacksaw through a pipe and plug the ends and then run back to my experiment. I'd have three or four watches on with alarms set to different things that I'd have to run back to. So I was multitasking in order to try to get everything accomplished".

Jerry Linenger, US astronaut, describing life aboard the Mir space station (BBC T.V. "Horizon" programme, 23 April 1998).

The literature suggests that the cognitive processes underlying performance in these sorts of situations may be selectively impaired in some neurological patients. Thus Shallice and Burgess (Shallice, Burgess et al., 1993) reported three patients who had all suffered frontal lobe damage and who showed marked impairments in everyday life activities despite little or no detectable impairment on a range of traditional neuropsychological tests, including those of executive abilities previously shown to be sensitive to frontal lobe dysfunction. The disability took specific forms. The patients were impaired primarily on tasks that involved prioritisation, organisation and execution of a number of different tasks within a given period. Shallice and Burgess (1991) argued that a key component of successful performance in these situations was the ability to create and activate delayed intentions. The successful performance of the patients on the traditional tasks was explained as not being relevant to the patients' deficits since they did not tap these particular functions, in contrast to everyday life activities such as shopping or preparing a complex meal, which often involve the prioritisation of competing demands and the creation, maintenance and activation of delayed intentions. Shallice and Burgess (1991) were by no means the first or last to

have reported this “strategy application disorder”. Eslinger and Damasio (1985), Goldstein et al. (1993) and Duncan et al. (1995) have also reported other striking cases with similar patterns. These authors have offered a variety of explanations for their patients’ patterns. Goldstein et al. (1993) gave an analysis in terms of the model of Shallice and Burgess, but Damasio and his colleagues (Damasio, 1996; Damasio et al., 1991; Saver & Damasio, 1991) have explained their patients’ problems in terms of the failure of a system which operates to signal the possible deleterious consequences of a course of action (the “somatic marker hypothesis”). Duncan et al. (1995) took yet another view, characterizing the patient’s deficits in terms of “goal neglect” a phenomenon related to Spearman's “9” (1927). The basic empirical findings concerning these patients are however somewhat more agreed. Many of the more recent studies have used as least one of the two measures developed in the Shallice and Burgess (1991) study (the “six element” and the “multiple errands” tests), and all cases to whom they have been administered have failed at least one of them. The multiple errands test (MET) is a real-life task based around a shopping precinct. Participants are given some money and an instruction sheet and asked to buy various items, find out certain information, and be at a certain location at a specific time, whilst observing a number of rules such as “you must not enter a shop other than to buy something” which emphasizes the planning and prospective memory demands of the task. The second task, the six element test (SET), was designed to tap a subset of the same cognitive components, but do, so under more controlled and easily quantifiable conditions. Subjects were presented with three subtasks; each split into two sections. They were told that they were not permitted to carry out the first section of a given subtask followed by the second section of the same task, and that earlier items within a task scored more points than later ones. They were told that otherwise they were free to organize their efforts in any way they saw fit with the overall objective being to score as many points as possible within a permitted period. Burgess et al. (1998) provided further empirical evidence that patients with these sorts of everyday life problems tend to perform poorly specifically on these multitasking tests, and also that the cognitive process(es) damaged in these patients may usefully be regarded as constituting a

discrete cognitive system. Burgess et al. (2000) proposed a model where there are three cognitive constructs (i.e. sets of processes or brain systems) which work together to facilitate multitasking. One cognitive system is primarily involved in the retrospective memory demands of the task (e.g. rule learning and remembering); a second system, whilst drawing upon the resources of the first, is separate from it, and is used in planning; and the third cognitive system facilitates the prospective memory demands of the task. This system is crucial to plan- and rule-following, task switching and is also related to being able to accurately recount what one has done. The most general conclusion from the anatomical behavioural analysis is that the involvement of a medial left-hemisphere region principally involving the posterior cingulate (Brodmann's areas 23 and 31) but also extending deep into the occipital lobe was associated with impairments to both retrospective (e.g. rule learning) and prospective (e.g. plan-following) components of our task. Involvement of the left anterior cingulate and surrounding white matter regions gave rise to problems in remembering the task rules after a delay. Right dorsolateral frontal lesions (Brodmann areas 8, 9, 46) gave deficits in planning. Poor overall task performance, using a score that heavily penalizes rule-breaking behaviour, was produced by lesions not only to the posterior cingulate area previously mentioned, but also by involvement of left medial frontal regions (the more polar and medial (but not orbital) aspects) of Brodmann areas 8, 9 and 10.

1.6 Overall summary on adult neuropsychological literature

Executive functions, higher-level cognitive functions involved in the control and regulation of lower cognitive operations, are clinically assessed by a small battery of tests that, on the basis of putative sensitivity to frontal damage, are referred to as "frontal." Support for the validity of this claim is variable. There is evidence for the sensitivity of these measures to right or left DLPFC, and in many instances to superior medial area lesions. In some cases this claim is supported by functional neuroimaging data. Because these tests are complex and multifactorial, they do not specifically assess frontal function. Both lesion and functional neuroimaging evidence indicate

recruitment of posterior regions involved in the basic linguistic or perceptual operations of the task. Moreover, task complexity could affect which regions of the frontal lobes were involved. As a general rule for some processes, the more complex the function, the more frontal brain regions involved (Stuss et al. 1994, 1999). In general, modern cognitive neuroscience findings have failed to penetrate clinical assessment of executive functions. The incorporation of measures with greater psychological and anatomical specificity into modern clinical neuropsychology would improve executive functioning assessment. Whether modern or standard, however, a very consistent finding is the relative insensitivity of these measures to VPFC damage.

1.7 Development of frontal lobe processes

Parallels between ongoing maturation of the frontal lobes and the emergence of executive capacities have been reported in a number of studies. These results suggest that, where developmentally appropriate assessment tools are employed, evidence of executive skills can be elicited in children younger than 6 (Anderson, Anderson, & Lajoie, 1996; Bruner, 1973; DeLoache & Brown, 1984; Dennis, 1991; Diamond, 1990; Diamond & Goldman-Rakic, 1989; Goldman-Rakic, 1987; Klahr, 1978; Klahr & Robinson, 1981; Levin et al., 1991; Passler, Isaac, & Hynd, 1985; Welsh, Pennington, & Groisser, 1991). Klenberg, Korkman & Lahti-Nuuttila (2001) showed that in 3 years old children inhibitory functions precedes the development of more complex functions selective attention, and EFs continue to develop into adolescence (Davidson, Amso, Anderson & Diamond, 2006). There is now growing evidence that children sustaining brain damage exhibit deficits in executive skills. Such problems may interfere with the child's capacity to develop normally and interact effectively with the environment, thus leading to ongoing cognitive, academic, and social disturbances (Anderson & Moore, 1995; Dennis, 1989). It is now well established that cerebral development is ongoing during childhood. Brain weight increases from around 400 grams at birth to 1500 grams at maturity in early adulthood, although most maturation is thought to occur during the first decade of life (Caeser, 1993). While pre-natal development is

primarily concerned with structural formation, post-natal development is associated with elaboration of the CNS (Orzhekhovskaya, 1981; Yakovlev, 1962). In particular, processes such as dendritic aborisation, myelination, and synaptogenesis have all been reported to progress during early childhood, in a largely hierarchical manner, with anterior regions the last to reach maturity (Fuster, 1993; Jernigan & Tallal, 1990; Kolb & Fantie, 1989; Risser & Edgell, 1988). Initially developmental neuropsychology was influenced by a view that the frontal lobes were "functionally silent" in infancy and early childhood, with executive skills not measurable until the second decade of life. A number of neuropsychological studies now refute this view, documenting frontal lobe activity even in infancy. For example, Chugani, Phelps, and Mazziotta (1987) measured local cerebral metabolic rates of glucose in infants and young children, and found evidence of frontal metabolic changes in infants as young as 6 months of age. Similarly Bell and Fox (1992) have documented changes in scalp recorded electroencephalograms (EEGs) in frontal regions during the first year of life, relating these to improvements in behavioural performances. Many workers now support the notion that these biological growth markers may explain some of the age-related variation in "non-biological" development such as cognition (Caeser, 1993; Thatcher, 1991, 1992). It is generally agreed that the frontal lobes are hierarchically organised, with all areas receiving input from posterior and subcortical cerebral regions. In particular the prefrontal cortex, thought to be the primary mediator of executive functions, receives input from all areas of the frontal and posterior neocortex (Barbas, 1992; Fuster, 1993). Thus sensory and perceptual data are processed by the frontal lobes where actions are organised and executed. This pattern of connectivity suggests that while prefrontal regions may "orchestrate" behaviour, they are also dependent on all other cerebral areas for input, with efficient functioning reliant upon the quality of information received from other cerebral regions.

Development of the frontal lobes also appears to follow a hierarchical pattern, consistent with processes such as myelination which progress through a number of stages, from primary and sensory areas to association areas and finally frontal regions (Fuster, 1993; Hudspeth & Pribram,

1990; Staudt et al., 1993). Vestibular and spinal tracts, related to basic postural control, are myelinated as early as at term. Midbrain cortical–visual pathways show evidence of myelination by 2–3 months of age and descending lateral cortical spinal tracts by the end of the first year of life, when fine motor control appears (Caeser & Lagae, 1991). Cerebellar–cerebral connections are not myelinated until the second year of life, with reticular tracts still maturing at school age and tracts connecting specific and associative cortical areas showing ongoing development into adulthood (Yakovlev & Lecours, 1967).

Results from EEG studies also indicate CNS changes through childhood. Thatcher (1991, 1992) has described a number of growth periods, the first between birth and 2 years, another from 7 to 9 years, with a final spurt in late adolescence (16–19 years). These growth spurts are thought to be associated with increases in either the number or strength of cortical synaptic connections. Consistent with Thatcher's findings, Hudspeth and Pribram (1990) document EEG data which indicate maturational peaks and plateaux continuing through childhood and into adolescence. They report a differential progression of regional cerebral development, with simultaneous completion of maturation throughout the CNS. In frontal regions, they describe accelerated development from 7 to 10 years which then terminates synchronously with development of other brain regions. Age-related pre-frontal ribonucleic acid and development, through to approximately 9 years of age (Uemura & Hartmann, 1978), and changes in patterns of metabolic activity and levels of various enzymes (Kennedy, Sakurada, Shinohara, & Miyaoka, 1982), also support a hierarchical model of frontal lobe development. It may be that not all CNS development conforms to this hierarchical model.

An alternative argument suggests that while measurable parameters behave in a spurt-like fashion, underlying development is essentially continuous (Stuss, 1992). For example, synaptogenesis appears to be simultaneous in multiple areas and layers of the cortex (Rakic et al., 1986), with neurotransmitter receptors throughout the brain reported to mature at the same time (Lidow & Goldman-Rakic, 1991). Such findings suggest concurrent development, where posterior and anterior structures develop along approximately the same timetable. Not all research supports

this view of simultaneous maturation even for neurochemical markers, with some arguing that this pattern, while present in non-human species, may not hold for humans (Gibson, 1991). Clearly, there is a need for further research to delineate these complex issues. To summarise, these various lines of inquiry suggest that cerebral development is likely to be primarily hierarchical, both within and across cerebral regions, with frontal areas reaching maturity relatively late, in early puberty. Further, there is some support for a step-wise model of development, rather than a gradual progression, with convergent evidence that growth spurts occur in early infancy, again around 7–10 years of age, with a final spurt during adolescence.

From a psychological point of view, using measures of executive functioning adapted from adult neuropsychology, Passler, Isaac, and Hynd (1985) shown that children as young as 6 years are able to exhibit strategic behaviour and planning skills. Their results suggest a stage-like progression of executive skills, with mastery still not achieved by the age of 12. In a follow-up study, Becker, Isaac, and Hynd (1987) report a similar pattern of results, once again noting a failure to achieve adult levels on executive measures by the age of 12. Using the Wisconsin Card Sorting Test as their measure of executive function, Chelune and Baer (1986) report improvements in performance between 6 and 10 years, with adult performance achieved by 12 years. Further, they observed that 6-year-old children demonstrated difficulties similar to those seen in adults with focal frontal lesions! A number of researchers have employed a "battery model", administering a range of tests purported to measure executive function. Such an approach, while providing developmental trajectories for each of these tasks, also enables investigation of possible relationships among measures, thus addressing the crucial issue of test validity. Levin and his colleagues (Levin et al., 1991) evaluated 52 normal children and adolescents in three age bands, 7–8 years, 9–12 years, and 13–15 years. They administered a range of "executive" measures and identified developmental gains across all tasks, reflecting progress in concept formation, mental flexibility, planning and problem solving through childhood. Although their sample size was relatively small, they performed principal components analysis on their data, identifying three factors which they argued

were associated with specific aspects of executive function, as well as unique developmental patterns. Factor 1 tapped semantic association/concept formation and Factor 3 was primarily concerned with problem solving, with each of these abilities showing a gradual progression over the three age ranges. Factor 2 was related to impulse control and mental flexibility and these behaviours were noted to reach adult levels by the age of 12. Welsh, Pennington, and Groisser (1991) also studied a sample of normal children, aged from 3 to 12 years, using a series of measures of executive function. Consistent with previous findings, their results provide evidence for stage-like development, with some components of executive function maturing earlier than others, thus supporting a multidimensional notion of executive function. They argue for three distinct developmental stages, the first commencing around age 6, a second about age 10, and a final spurt in early adolescence. They suggest that the ability to resist distraction is the first skill to mature, at around age 6. Organised search, hypothesis testing, and impulse control appear to reach adult levels at around age 10, with verbal fluency, motor sequencing and planning skills not at adult levels at age 12. They further investigated possible associations among their measures, and identified three discrete factors. Factor 1, described as representing speeded responding; Factor 2, an indicator of hypothesis testing and impulse control; and Factor 3, reflecting planning ability. Anderson, Lajoie, and Bell (1995) employed a similar methodology, with the primary aim of providing normative data for a number of commonly used clinical tests, purported to measure executive functions. Their sample included 376 children aged 7–13 years, selected to be representative of the general population with respect to social factors and gender. In line with the work of Levin et al. (1990) and Welsh et al. (1991), results suggest continued significant improvements in test performance through middle childhood, indicating ongoing gains in executive functions. An examination of correlations among these executive measures, suggest relatively strong associations between tasks tapping problem solving and planning ability; in contrast, only a weak relationship was found between these measures and tests of concept formation.

Anderson (1998) analysed the development of the performance of some classical frontal tasks used in pediatric neuropsychology: from 7 to 13 years of age. Considering different tests: Planning Abilities (Rey-Figure), Problem-Solving (Tower of London and Tower of Hanoi), Abstraction and Concept Formation (Verbal Fluency and Twenty Question task) and Mental Flexibility (Wisconsin Card Sorting Test, Trail Making Test and Stroop test), she showed that the development of EF is linear from 7 to 12 years old, when the performance of children is comparable to that of young adults. A different position was held by Klenberg, Korkman & Lahti-Nuuttila (2001) who obtained data from 10 subtests measuring impulse control and inhibition of irrelevant responses, auditory and visual attention, visual search, planning, and verbal and visual fluency in children aged 3-12 years. According to their factor analysis, inhibition, auditory attention, visual attention, and the EF of fluency clustered into separate factors. These authors showed that the development proceeded sequentially, from motor inhibition and impulse control to functions of selective and sustained attention, and finally to EFs of fluency: EFs are highly interrelated cognitive functions but their developmental sequences are distinct from each another. Finally, Davidson et al (2006) showed that in children between 4 to 13 years working memory, inhibition and cognitive flexibility have different rates of development.

1.8 Conclusive considerations on executive function studies with children

Theoretical models of executive function (e.g. Shallice and Burgess, 1991) make specific predictions about the behavioural consequences of impaired executive control. These include: distractibility, impulsivity, and preservative errors in the face of changes to a routine situation. These problems are all highly characteristic of the everyday difficulties experienced by individuals with ADHD. Moreover, other studies have shown that 'hard-to-manage' pre-schoolers at risk for ADHD also perform poorly on simple tests of executive function (Hughes et al., 1998; Speltz, et al., 1999). Group differences in executive function are also apparent when 'hard to manage' children (at risk for ADHD) are either followed-up over a 3-year period or recruited from a slightly older age-

group. Brophy et al. (2002) indicated that 7-year-olds identified as 'hard to manage' at age four continue to show impaired inhibitory control (on a Go No-Go task), but no longer display performance deficits on tests of planning (Tower of London) and working memory (subject ordered search). These results mirror findings from a study by Charman et al. (2001) in which a clinical sample of 6–10-year olds with ADHD showed impaired inhibitory control (on a Go No-Go task), but intact planning (Tower of Hanoi). Perner et al. (2002) results do not fit neatly into the above picture, since the 'hard-to-manage' children in the Perner et al. (2002) study showed poor planning (Tower of London), but no significant impairment in inhibitory control (Go No-Go). How should the discrepancies between these findings be explained? In their discussion, Perner et al. (2002) outlined a number of methodological contrasts between the studies and noted that adopting more similar methods of analysis reduced (but did not remove) these discrepancies These residual differences may reflect sample contrasts. In particular, Perner's sample was younger than Brophy et al. (2002) sample, and closer in age to the sample in the Hughes et al. (1998) original study, which produced quite similar results. The possibility that different aspects of executive function become salient at different ages has already been raised in relation to children with autism (Hughes, 2001) and deserves further research.

One factor that could lead to an age contrast in study findings (such as that posited above) is task complexity. For example, because of their complex rules and instructions, tower planning tasks may be sensitive to impairments in younger but not older children at risk for ADHD. This point is in keeping with a similar point raised by Beveridge et al. (2002), concerning the disproportionate effect upon younger children of increasing the working memory or inhibitory control demands of a given task. In many ways then, because of their relatively limited executive capacities, young children are ideal candidates for evaluating theoretical predictions (e.g. concerning the relationship between specific executive functions). However, the main methodological point to emerge from the Beveridge et al. paper (2002) is that theories are best tested through direct manipulation of task parameters, rather than via the more commonplace but statistically noisier approach of relying upon

correlational evidence.

Another reason for the developing interest in the development of executive function is that studies of children provide an opportunity to tease apart distinct components of executive control. Studies of adult clinical populations typically require complex, multi-componential tasks; as a result, different groups may perform equally poorly for different reasons. This lack of discriminant validity is a key problem for researchers in this field. Investigations with children require simplified tasks that have the benefit of being easier to interpret. In addition, manipulating task parameters may be especially fruitful in studies of children, since their relatively limited processing capacity makes them more sensitive to effects of increased demands for particular functions.

Chapter 2

What is Attention Deficit Hyperactivity Disorder (ADHD)

Attention-Deficit/Hyperactivity Disorder (ADHD) is the current label for one of the most prevalent and intensively studied syndromes in child psychiatry, and possibly the most controversial. It is conservatively estimated to occur in 3% to 5% of children from diverse cultures and geographical regions, with an overrepresentation of boys by approximately 3:1 (e.g. Anderson, Williams, McGee, & Silva, 1987; Baumgartel, Wolraich, & Dietrich, 1995; Biederman & Faraone, 2005; Bird et al., 1988; Rohde et al., 2005; Szatmari, Onord, & Boyle, 1989; Wang, Chong, Chou, & Yang, 1993). ADHD encompasses the life span, affecting children from preschool to school age and continuing through adolescence into adulthood, albeit with age - and gender - related changes in its manifestation (e.g. Barkley, Fischer, Edelbrock, & Smallish, 1990; Biederman et al., 1996a; Caspi, Moffitt, Newman, & Silva, 1996; Kessler et al, 2005; Klein & Manuzza, 1991; Schoechlin & Engel, 2005; Weiss & Hechtman, 1993). The core behavioral symptoms of inattention, impulsiveness, and hyperactivity cause significant impairment in family and peer relationships and the ability to succeed in school during childhood and increase the risk for social isolation, serious driving accidents, and additional psychopathology in adolescence and adulthood (e.g. Barkley, Murphy, & Kwasnik, 1996; Biederman et al., 1995; Braaten et al., 2003; Nada-Raja et al., 1997; Weiss & Hechtman, 1993). Currently, the *Diagnostic and Statistical Manual of Mental Disorders-IV* (*DSM-IV-TR*; APA, 2000) defines ADHD based on elevations of two separate but correlated symptom dimensions, those of inattention (IA) and hyperactivity/impulsivity (H/I). Children meet criteria for the disorder by having six or more symptoms of either IA or of H/I, or both. Hence, *DSM-IV* describes three diagnostic subtypes of ADHD based on differential elevations of symptoms on these two dimensions. The first is Predominantly Inattentive subtype (ADHD-IA), in which children have six or more symptoms of IA but fewer than six symptoms of H/I, the second is Predominantly Hyperactive/Impulsive subtype (ADHD-HI), in which children have six or more

symptoms of H/I but fewer than six symptoms of IA, and the third is Combined subtype (ADHD-C), in which children show elevations of six or more symptoms on both dimensions. The *DSM-IV* field trials indicated that the current subtypes differ significantly on variables such as age of onset, gender ratio, and level of social and academic impairment (Lahey et al., 1994). Other researches also suggests that the subtypes may differ in rates of comorbidity with other childhood disorders (Counts, Nigg, Stawicki, Rappley & Von Eye, 2005; Eiraldi, Power, & Nezu, 1997; Faraone, Biederman, Weber, & Russell, 1998; Gadow et al, 2004; Willcutt, Pennington, Chhabildas, Friedman, & Alexander, 1999).

ADHD is a true biopsychosocial disorder, raising critical questions concerning the relations between genetic, biological, and environmental factors. As a result, it has captured the interest of clinicians and researchers from many different disciplines continuously for four decades (Biederman & Faraone, 2005). The literature is voluminous. For example, the *Medline* and *Psychlit* databases each list approximately 5000 peer reviewed articles published since 1966 and 1967, respectively. As a result, a comprehensive review of all aspects of ADHD is no longer feasible. Nonetheless, the extant literature is providing preliminary evidence for dysfunction of the frontostriatal networks (which control attention and response organization) that may be of genetic origin. These findings are generally consistent with current models of ADHD that are rooted in biological paradigms and emphasize neurobiological, neuroanatomical, and genetic mechanisms as contributing factors to the behavioral characteristics (e.g. Barkley, 1997; Castellanos & Tannock, 2002; Quay, 1988; Tannock, 1998).

2.1 North American versus European Concepts of ADHD

For the past three decades, ADHD has been conceptualized as comprising three core clusters of behavioral symptoms: poor sustained attention, impulsiveness, and hyperactivity (American Psychiatric Association, 1980, 1987; World Health Organization, 1978; 1992). Clinicians and researchers in North America and Europe have differed in the emphasis placed on these various

symptom clusters, the requirement for pervasiveness of symptomatology, and the relative weight given to other concurrent problems and psychopathology. Moreover, they have differed in their conceptualization of the developmental significance of ADHD. For example, in North America ADHD is viewed as a common but heterogeneous developmental disorder causing significant impairment, whereas in Europe the diagnosis (i.e. of hyperkinetic syndrome) is reserved for ADHD uncomplicated by comorbid psychopathology. Defined in that way, the condition is relatively rare and not thought to confer risk for development. These international differences in conceptual, diagnostic, therapeutic, and research approaches to ADHD have been well-documented by Sergeant and Steinhausen (1992). Further conceptual shifts have occurred on both sides of the Atlantic, but these changes may not reduce the international gap. From the European perspective, there is growing recognition that hyperactivity itself carries a risk for later development, whether or not conduct disorder is also present (Taylor, 1994, 1995). This change in thinking about the developmental significance of the disorder has been motivated primarily by findings from longitudinal epidemiological studies in Britain and New Zealand (e.g. Fergusson & Horwood, 1993; McGee et al., 1991; Taylor, Sandberg, Thorley, & Giles, 1991) and by epidemiological and clinical studies emerging from the European Network on Hyperkinetic Disorders (Eunethydis; Sergeant, 1995; Sergeant & Steinhausen, 1992). In North America, the growing concern with the heterogeneity of ADHD is reflected by the delineation of subtypes based on the pattern of symptom clusters (American Psychiatric Association, 2000) and by the preoccupation with the significance of comorbidity. Based on findings from empirical research and factor analysis (Gomez, Burns, Walsh & De Moura, 2003; Lahey et al., 1988; Zuddas et al., in press), two symptoms clusters instead of three are delineated. Specifically, symptoms of inattention are distinguished from symptoms of impulsiveness and hyperactivity, which are now conceptualized as a single cluster. The risk associated with ADHD is thought to reside in the impulsivity/hyperactivity symptom cluster (Barkley, 1994, 1997; Quay, 1997). The delineation of two symptom clusters, which are thought to be distinct in terms of their etiology, clinical course, correlates, response to treatment, and outcome

(Chhabildas, Pennington & Willcutt, 2001; Lahey et al., 1994), yields three subtypes of ADHD: predominantly inattentive, predominantly hyperactive-impulsive, and a combined type. This conceptual shift has not been adopted universally. Clinical and research communities in Europe that use criteria from the International Classification of Diseases (ICD-10) continue to require all three types of symptoms to be present.

2.2 Comorbidity

Research documenting the types and rates of comorbidity and its theoretical and clinical implications has grown exponentially during last decade. Between 50% and 80% of children with ADHD also meet diagnostic criteria for other disorders, with rates of comorbidity varying according to the sample studied and the method of ascertainment (reviewed by Biederman, Newcorn, et al., 1991; Jensen et al., 1997; Spencer, Biederman & Wilen, 1999). The most frequently observed comorbidity is between ADHD and other disruptive behavior disorders, with oppositional defiant disorder and conduct disorder occurring in approximately 40% to 90% of cases (reviewed by Newcorn & Halperin, 1994; Plizka, 1998; Jensen et al., 1997). Comorbidity between ADHD and internalizing disorders and between ADHD and developmental learning disorders is also common. For example, notwithstanding some disagreements, the data suggest that 15% to 20% of children with ADHD have concurrent mood disorders, approximately 25% have comorbid anxiety disorders, and about 30% have specific learning disabilities (Biederman, 2005; Biederman, Newcorn, et al., 1991; Hinshaw, 1992; Jensen, Martin & Cantwell, 1997; Russo & Beidel, 1994). However, few studies specify whether the figures reflect comorbidity between ADHD and one other disorder independent of or in conjunction with other comorbid diagnoses. The manifestation of ADHD with more than one comorbid diagnosis (e.g. ADHD with comorbid anxiety plus conduct disorder; ADHD with comorbid anxiety, conduct disorder, and reading disorder) is not uncommon (e.g. Anderson, Williams, McGee & Silva, 1987; Biederman, 2005; Biederman et al., 1996b; Faraone, Sergeant, Gillberg & Biederman, 2003; Livingstone, Dykman, & Ackerman, 1990). Comorbidity

rates will differ in North America and Europe because the two classification systems differ in how they handle co-occurring disorders. For example, the American DSM system encourages the use of multiple diagnoses (albeit some hierarchical rules at the level of individual diagnoses are followed), but the comorbid condition is not presumed to be a distinct disorder. By contrast, the International ICD system encourages a parsimonious approach that afford a single diagnosis, with some codes for mixed disorders (e.g. hyperkinetic conduct disorder), which carries an implicit assumption that there is a uniqueness about the co-occurring disorders that warrants a separate diagnosis. High rates of comorbidity in general, as well as with ADHD in particular, challenge the current nosological systems and suggest the need to examine the evidence for new diagnostic constructs (Caron & Rutter, 1991). Evidence that the comorbidity occurs more frequently than the component disorders alone occur by chance, or that the comorbidity arises from a unique set of risk factors, or that it conveys unique treatment or prognostic information, is required to validate a new diagnostic construct. Jensen and colleagues (1997) applied Cantwell's model in a review of comorbidity in ADHD. They concluded that two new ADHD subtypes warrant delineation: an aggressive subtype and an anxious subtype. This conclusion is based on the extant literature that suggests that the co-occurrence of either conduct disorder or anxiety disorder with ADHD *interacts with and alters* this diagnostic construct in important ways, including its typical clinical phenomenology, psychological characteristics, psychosocial factors, clinical course and outcome, and treatment response. For example, when ADHD is comorbid with conduct disorder, both the neuropsychological deficits (especially in verbal and memory domains) and the outcomes (in terms of drug use and abuse, driving-related accidents, and additional psychiatric comorbidity) appear to be worse than those associated with either ADHD or conduct disorder status alone (Barkley, Guevremont, Anastopoulos, DuPaul, & Shelton, 1993; Barkley et al., 1996; Halperin et al., 1990; Herrero, Hechtman, & Weiss, 1994; Mannuzza, Klein, Bessler, Malloy & LaPadula, 1993; Moffitt, 1990). Moreover, there is evidence that stimulant medication may not be as effective in reducing motoric activity in children with the aggressive type of ADHD compared to non aggressive ADHD (Matier,

Halperin, Sharma, Newcorn, & Sathaye, 1992). Similarly, there is accumulating evidence that the presence of comorbid anxiety alters the therapeutic risk benefit ratio of psychostimulant treatment of ADHD (reviewed by Tannock, Ickowicz, & Schachar, 1995). For example, highly anxious children with ADHD exhibit a less robust behavioral response and minimal or no improvements in working memory, in comparison with a non-anxious ADHD group. On the other hand, children with this comorbid condition are at greater risk for the side effects of stimulant medication (DuPaul, Barkley, & McMurray, 1994; Pliszka, 1989; Tannock, Fine, Heintz, & Schachar, 1995; Tannock, Ickowicz, et al., 1995; Urman, Ickowicz, Fulford, & Tannock, 1995).

2.3 Attempts to understand the enigma: current neurocognitive models

Despite the great scientific interest it has aroused, Attention-Deficit/Hyperactivity Disorder (ADHD) remains among the least well characterised of mental disorders. This phenomenon could be due to the heterogeneity of its clinical expression and its multi-factorially determined etiology makes achieving the sort of theoretical unity required by such models of ADHD unlikely.

2.3.1 The behavioral inhibitory deficit model by Barkley

Barkley (1997) argued that the multiple deficit observed in ADHD, including apparent attentional problems, can be traced to a single cardinal feature: an impairment in the development of delayed responding or response inhibition. According to his model, children with ADHD suffer primarily of a Behavioral Inhibitory Deficit that influences four types of Executive Processes: Working Memory, Self-regulation of affect, arousal and motivation, Reconstitution and Internalization of speech. These four impaired systems lead to a deficit to the motor control. Barkley (1997) differentiated and listed specific functions included in each impaired system. Behavioral inhibition was conceptualized as the ability to inhibit prepotent response, to stop an ongoing response and to control interference. Working memory deficits were related to the ability

to hold events in mind, manipulating or acting on the events, imitating complex behavior sequences, having sense of time, demonstrating good prospective and retrospective functions, and showing skills of cross temporal organization of behaviors. Self-regulation of affect, motivation and arousal is the summary of different abilities, such as emotional self-control, self-regulation of motivation, ability to have a social perspective, and the regulation of arousal in the service of goal directed actions. Internalisation of speech describes the ability to self-describe, to follow specific instructions and rules, to solve problems via self-questioning, to generate moral reasoning. Finally, Reconstitution describes the ability to analyse and synthesise behaviors, to be fluent in verbal production and complex behavior, to have a goal directed creativity. These four impaired systems lead to difficulties in motor control that include the ability to inhibit task irrelevant responses, to execute goal directed responses, to execute novel and complex motor sequences, to be sensitive to feedback, to be able of behavior control by internally represented information. In figure 2.1 a schematic representation of this model is presented.

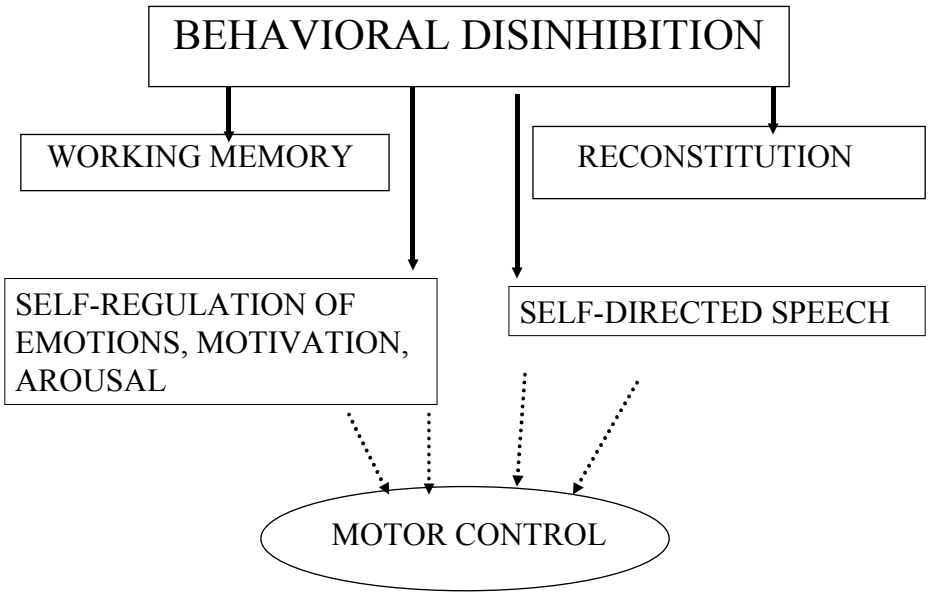


Fig. 2.1. Schematic representation of Barkley's model (1997)

2.3.2 The cognitive-energetic model by Sergeant and Van der Meere

From the results of vigilance and human performance research, Sergeant & Van der Meere (1994) proposed the Cognitive – Energetic Model to explain the complex pattern of deficit shown by children with ADHD. The authors differentiated the State Factors from the Computational Factors, the formers include three energetic pools: effort, arousal and activation; the latters include four general stages: encoding, search, decision and motor organization, as proposed by Sternberg (1999). The Effort was conceived of as the necessary energy to meet task demands. The Arousal was defined as a phasic responding that is time locked to stimulus processing; typical variables influencing arousal are signal intensity and novelty (Sanders, 1983). Tonic changes of physiological activity were thought to represent the operation of the Activation (Pribram & McGuinness, 1975). The cognitive – energetic model also includes an overriding evaluation mechanism. This mechanism is associated with planning, monitoring, detection of errors and their correction. Thus, the model has three levels: a lower stratum with four stages of cognitive processing, a middle level of with three energetic pools, and a higher level with mechanism of management or control. This model had been proposed in combination with a review of twelve tasks measuring different types of inhibitory processes but the two components (Energetic and Inhibition Dysfunction) had not been integrated each other in the description of the model. According to Sergeant et al. (1999), disinhibition has been conceptualized as: 1) fast but inaccurate responding; 2) response perseveration; 3) failure to responde appropriately in a response conflict task. According to Sergeant et al. (1999) proposal, only 3 of the 12 tasks clearly discriminate children with ADHD from Controls (Go/no-go task, Stop signal task, Change task). The authors concluded that it is an oversimplification to claim that ADHD children uniquely suffer from a inhibitory deficit (Barkley, 1997) that account for all experimental findings of impaired performance on a myriad of tasks. A schematic representation of the model is depicted in figure 2.2.

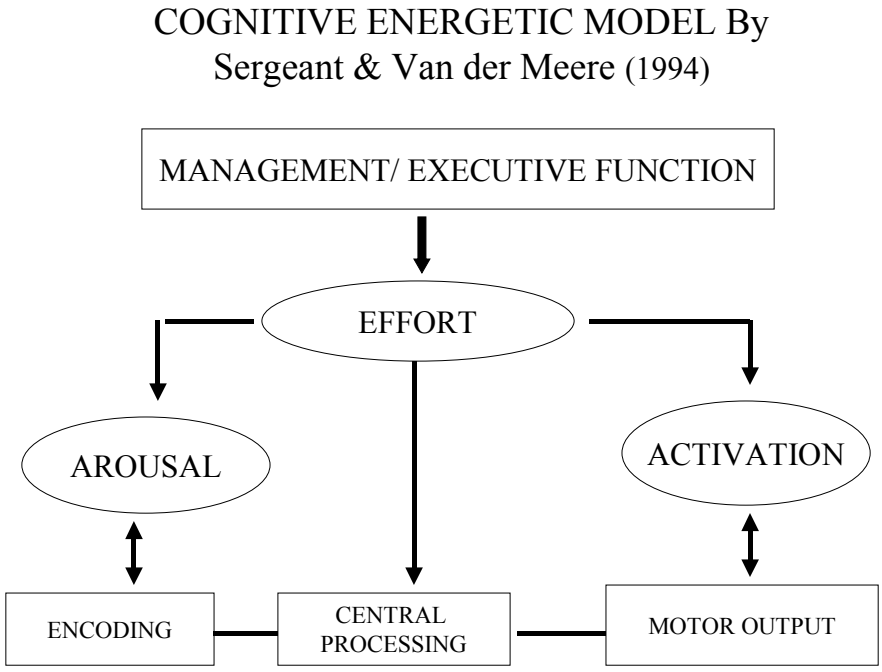


Fig. 2.2. Schematic representation of the Cognitive – Energetic Model by Sergeant and Van der Meere (1994).

2.3.3 The Attentional Networks model by Swanson and Posner

Posner and Petersen (1990) offered a theory of attention based on the working hypothesis that distinct neural networks accomplish component processes of alerting, orienting, and executive control. *Alerting* consists of suppressing background neural noise (by inhibiting ongoing or irrelevant activity and mental effort to establish a state of vigilance) to establish readiness to react. *Orienting* consist of mobilizing specific neural resources to prepare to process an expected type of input. *Executive control* consists of coordinating multiple specialized neural processes to direct behavior toward a goal. Posner and Petersen proposed that the three neural networks (Alerting, Orienting and Executive Control) are localized on specific regions of the cortex: right dorsolateral prefrontal cortex, anterior cingulate and posterior parietal lobe respectively. The alerting processes and right frontal network operate to establish *sustained attention*; the orienting and posterior parietal network operate to establish *selective attention*; the executive control and anterior cingulate network operate to establish *divided attention.*

Swanson, Posner et al. (1998) postulated that the three broad domains of ADHD symptomatology, namely inattentive-orienting, inattentive-alerting, and hyperactive/impulsive are linked to the three different neural networks. Their proposal is based on an alignement of clinical, cognitive and neural level of analysis using three paradigms and analysing different type of errors produced by ADHD subjects. The Inattentive-Alerting domain includes the following symptoms: Difficulty in sustaining attention, Failure to finish activity, Avoiding sustained effort, and are correlated to Continuous Performance Task (CPT) results. The Inattentive-Orienting domain includes these symtoms: the child is distracted by irrelevant stimuli, does not seem to listen, fails to give close attention to details, and are correlated to performance on Visuo-spatial Orienting Task (VOT). Finally the Hyperactive-impulsive domain includes these symptoms: the child blurts out answers, interrupt or intrudes, can't wait, and correlated to performance on Conflicting Resolution Task (CRT), such as Stroop. According to Swanson, Posner et al (1998) model, children with ADHD show more difficulty on CPT and CRT but less on VOT, thus the Alerting and Executive Control networks are more impaired than the Orienting one. From a localization perspective, Swanson, Posner et al (1998) ADHD is characterized by a dysfunction of on Right Prefrontal Cortex and on Anterior Cingulate Gyrus, in conjunction with localized impairments in Basal Ganglia, not further specified in their model.

2.3.4 The Dual Pathway model by Sonuga-Barke (2002)

Sonuga-Barge (2002) proposed a model that considers two different pathways. In one, ADHD is a disorder of dysregulation of thought and action associated with diminished inhibitory control. In the other, it is a motivational style (delay aversion) associated with fundamental alterations in reward mechanisms. Neuropsychological studies converge on the view that ADHD is associated with problems of executive or higher order control functions (Barkley, Grodzinsky & DuPaul, 1992; Sergeant et al., 2002; Willcutt et al., 2005). ADHD children lack attentional and strategic flexibility, display poor planning and working memory and fail to effectively monitor their

behaviour (Clark, Prior & Kinsella 2000; Cepeda, Cepeda & Kramer 2000). While such difficulties are shared with a range of psychopathologies the primary role of deficient inhibitory control in the emergence of this pattern of dysregulation seems to distinguish ADHD from other disorders (Barkley, 1997; Bayliss & Roodenrys, 2000; Ross, Harris, Olincy & Radant 2000). The best evidence in support of this assertion comes from the now large number of studies using the stop signal paradigm (SSP) (Schachar & Logan, 1990). This paradigm tests an individual's ability to inhibit an already initiated pre-potent response to a 'go signal' (typically visual) when signalled to do so by a 'stop signal' (typically auditory) presented at varying intervals prior to the expected time of the individuals 'go' response. Both the slope of the probability of inhibition given different stop intervals and the stop signal reaction time (SSRT) provide measures of the efficiency of inhibitory processes. A meta-analysis (Oosterlaan, Logan & Sergeant, 1998) and a number of subsequent studies (Schachar, Mota, Logan, Tannock & Klim, 2000; Nigg, 1999) show that ADHD children have a flatter probability of inhibition slope and longer SSRTs. These effects are of moderate to large size and appear consistent at least across clinical samples (Oosterlaan, Logan & Sergeant, 1998). The association of ADHD with deficient inhibitory control seems more robust than that with other executive functions (e.g. working memory) (Pennington & Ozonoff, 1996). While models emphasising disinhibtion and dysregulation dominate the current literature, a number of alternative accounts have been proposed that emphasise the motivational basis of ADHD (Haenlein & Caul, 1987; Zentall & Zentall, 1983; Johansen, Aase, Meyer & Sagvolden, 2002). The delay aversion hypothesis represents the most radical departure from the dominant neuropsychological paradigm (Sonuga-Barke, 1998). This model is based on the assumption that ADHD behaviours are functional expressions of an underlying motivational style rather than the result of dysfunctioning regulatory systems. According to this hypothesis ADHD children are motivated to escape or avoid delay. Their inattentive, overactive and impulsive behaviours therefore represent functional expressions of what has been termed delay aversion. The model predicts that when faced with a choice between immediacy and delay ADHD children will choose immediacy (Sonuga-Barke,

Taylor, Sembi & Smith, 1992), when no choice is available they will act on their environment to reduce their perception of time during delay by either creating or attending to non-temporal feature of the environment (Antrop, Roeyers, Van Oost & Buysse, 2000). The resulting behaviour, because of its likely task incompatibility, is labelled as inattentive and overactive. Sonuga-Barke's model (schematically represented in 1.3) describes ADHD as a developmental outcome of two quite distinct psychological/developmental processes. At a more abstract level, the model represents a reconciliation of two philosophically distinct views of behavioural disorder—one that seeks to identify the site of dysfunction in disorder while the other seeks to explore the role of function. One route characterises ADHD as predominantly a motivational style mediated by the emergence of delay aversion during childhood. The second sees it as predominantly a disorder of the regulation of thought and action resulting from inhibitory dysfunction. The emergence of ADHD symptoms is mediated by behavioural dysregulation while the effects on task engagement are mediated by cognitive dysregulation. Such cognitive dysregulation can be seen by the pattern of difficulties displayed by ADHD children on tasks requiring attentional flexibility, behavioural monitoring, planning and working memory. In the model there is no direct pathway between executive functions and ADHD symptoms. This reflects the more modest associations between measures of these functions and ADHD symptoms reported in the literature (Pennington & Ozonoff, 1996).

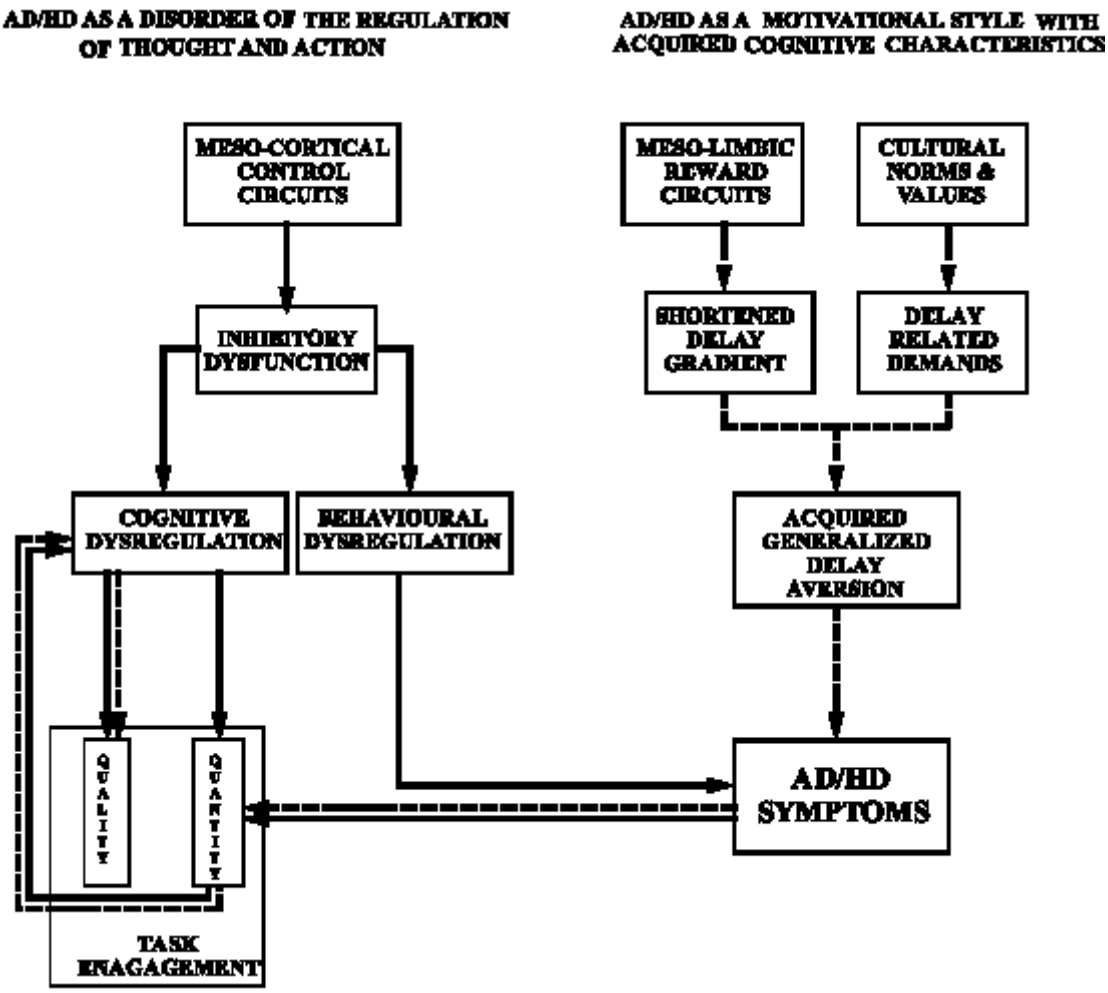


Fig. 2.3. A schematic representation of the dual pathway model of ADHD. The solid line represents the pathway for ADHD as a disorder of the regulation of thought and action. The dashed line represents ADHD as a motivational style.

In the model Dysregulation of Thought and Action Pathway - DTAP ADHD arises out of alterations within the higher order control circuits of the brain and therefore implicates the frontal and pre-frontal regions and their associated circuitry with projections from the basal ganglia and into the striatum being particularly important (Rubia, et al., 1999). Functions sub-served by this circuit are regulated by dopamine activity as part of a functionally and anatomically distinct meso-cortical branch of the dopamine system (Goldman-Rakic, 1992; Knable & Weinberg 1997) motivational style pathway (MSP -dashed line) provides an alternative route to ADHD. As

mentioned above delay aversion is not the core characteristic of the motivational pathway in this model. Rather, it is an acquired characteristic, which mediates the link between behavioural symptoms, task engagement and a more fundamental biologically based alteration in reward mechanisms (Johansen, Aase, Meyer & Sagvolden, 2002). In identifying altered reward mechanisms as underpinning this motivational style the model builds on evidence from animal studies showing that ADHD symptoms can result from a shortened 'delay of reward gradient' (Sagvolden & Sergeant, 1998; Sagvolden, Aase, Zeiner & Berger, 1998). This means that ADHD children discount the value of future events at a higher rate than other children. This leads to a preference for immediacy—i.e. behavioural impulsiveness.

Chapter 3

The neuropsychology of children with ADHD

3.1 Anatomic brain imaging studies of ADHD

Developing advances in structural and functional imaging techniques that permit the study of the human brain in vivo are leading to a new understanding of developmental neuropsychiatric disorders. Knowledge of the normal developmental changes and normal variability in the structure and function of the developing brain across childhood and adolescence is essential for the interpretation of differences associated with psychopathology. Studies of the structural morphometry in the developing brain, using techniques such as magnetic resonance imaging (MRI), indicate that the growth cycle of the human brain is complete by the middle of the second decade of life, but that gender-specific and age-related changes occur in the developing brain (Caviness, Kennedy, Bates, & Makris, 1996). Specifically, the brain volume of the school-aged female of ADHD children is smaller than that of the school-aged male: approximately 93% of the male brain volume (Filipek, Richelme, Kennedy, & Caviness, 1994). Also, the cerebral and cerebellar volumes appear to be larger in males, whereas the caudate size is disproportionately larger in females (Filipek et al., 1994; Giedd et al., 1996). Age-related decreases observed in the caudate and putamen and the age-related increases in lateral ventricular volume may be specific to males (Giedd et al., 1996). Moreover, bilaterally represented structures are generally symmetric and observed asymmetries are small in degree. For example, one study reported that, in ADHD subjects, the right cerebral hemisphere and caudate volumes were larger than the left, whereas the left lateral ventricles and putamen were larger than the right (Giedd et al., 1996).

In normal children, functional imaging studies of lifespan cortical development are yielding findings that support neo-Piagetian theories of cognitive development that propose cyclical, nonlinear, and dynamic patterns of growth rather than linear or monotonic growth (e.g. Case, 1987; Fischer & Rose, 1996; Van Geert, 1991). Analyses have revealed a cyclic lateralmedial and rostral-

caudal process of reorganization, with qualitatively different phase transitions in the left and right hemispheres (Thatcher, 1996). Moreover, Thatcher (1996, p. 104) proposes that "the iterative growth spurts and patterns of development during the post-natal period may reflect a convergence process which narrows the disparity between structure and function by slowly sculpting and shaping the brain's micro-anatomy to eventually meet the demands and requirements of an adult world". Evidence of normal variation in morphometric volumes and the dynamic cyclical changes during a relatively short span of years highlights the need for large gender-matched and age-matched cohort samples in pediatric neuropsychiatric studies (Giedd et al., 1996): few of the neuroimaging studies in ADHD meet these requirements. The common practice of aggregating cross-sectional data across inadequately matched, small samples of males and females in the 7-11-year age range may result in artifactual differences or obscure clinically important differences in developmental trajectories associated with psychopathology.

In ADHD research, the most commonly used techniques that focus on brain structure and anatomy include computerized transaxial tomography (CT) and magnetic resonance imaging (MRI). Functional/dynamic techniques used to study brain metabolism and regional change in brain activity include positon emission tomography (PET), single photon emission computerized tomography (SPECT), quantitative electrophysiology (QEEG) and evoked response potential (ERP), and functional magnetic resonance imaging (fMRI).

3.2 Structural Imaging Studies in ADHD

3.2.1 Total Cerebral Volume

Although the total size of the human brain is already 90-95% that of an adult by first grade (Sowell et al, 1999; Giedd et al., 1996; Reiss et al., 1996) the subcomponents of the brain continue to undergo dynamic changes throughout childhood and adolescence. White matter volume increases linearly, reflecting increasing myelination (Paus et al., 1999) and gray matter volume increases until early-to-mid-adolescence before decreasing during late adolescence, presumably from continued

synaptic pruning (Huttenlocher, 1979; Huttenlocher et al., 1997). Brain size is highly variable with as much as a twofold difference even among healthy people matched for age, sex, height, and weight (Lange et al., 1997). Total brain size in ADHD subjects is approximately 5% smaller than in age- and gender-matched controls (Castellanos et al., 1996; Castellanos et al., 2002).

3.2.2 Corpus Callosum

The corpus callosum is the largest interhemispheric commissure in the brain consisting of approximately 200 million mostly myelinated fibers connecting homologous areas of the left and right cerebral hemispheres. Because of the orientation and myelination of its fibers, the corpus callosum is readily identifiable on MR images and most research groups have started by quantifying its mid-sagittal area. Although total corpus callosum area has not differed from controls in any study, smaller anterior regions have generally been found (Hynd et al., 1991; Giedd et al., 1994; Baumgardner et al., 1996) in ADHD subjects.

3.2.3 Prefrontal Cortex

Smaller anterior corpus callosal areas are consistent with involvement of prefrontal cortical regions. Normally, the right anterior brain is slightly but consistently larger than the left (Weinberger et al., 1982). Significant decreases of this asymmetry in ADHD have been reported using computed tomography (Shaywitz et al., 1983) and MRI (Hynd et al., 1990; Filipek et al., 1997). Volumetric measures have also detected smaller right-sided prefrontal brain regions in boys with ADHD which were correlated with neuropsychological performance on tasks that required response inhibition (Casey et al., 1997).

3.2.4 Caudate Nucleus

The caudate nucleus and its associated circuits have long been suspected to play a pivotal role in ADHD (Pontius, 1973). Abnormalities of caudate nucleus volume (Castellanos et al., 1996;

Filipek et al., 1997) or asymmetry (Castellanos et al., 1996; Hynd et al., 1993; Mataro et al., 1997) have been reported although the studies differ in whether the normal caudate is asymmetric, and whether this asymmetry normally favors the right (Castellanos et al., 1996) or the left caudate (Filipek et al., 1997; Hynd et al., 1993; Mataro et al., 1997). These inconsistencies may reflect differences in methodology and comorbidity.

3.2.5 Putamen

Neither of the anatomic MRI studies that reported putamen volumes detected significant diagnostic group differences (Castellanos et al., 1996; Filipek et al., 1997) although statistical power was insufficient in one study to rule out type II error (Filipek et al., 1997).

3.2.6 Globus Pallidus

The output nuclei of the basal ganglia are the internal segment of the globus pallidus and the substantia nigra pars reticulata, but the volume of the latter cannot generally be measured with MRI, and the size of the globus pallidus can only be measured as a unit (lateral and medial segments together), and then only with difficulty. Still, this region has been found to be significantly reduced in size in ADHD subjects (Castellanos et al., 1996; Filipek et al., 1997), although these two studies differed in finding the larger difference on the left and right sides, respectively.

3.2.7 Cerebellum

An early computed tomography study found a trend towards greater cerebellar atrophy in adults with a prior history of hyperkinetic minimal brain dysfunction (Nasrallah et al., 1986). In a quantitative study of 112 subjects, the volumes of the cerebellar hemispheres were found to be significantly smaller in ADHD boys (Castellanos et al., 1996). In a follow-up study within the same sample, the cerebellar vermis as a whole, and particularly the posterior-inferior lobules (lobules VIII-X) were found to be significantly smaller in ADHD (Berquin et al., 1998) It is speculated that

dysfunction of the cerebello-thalamo-prefrontal circuit may underlie the motor control, inhibition, and executive function deficits encountered in ADHD.

3.3 Functional Brain Imaging Studies

PET with [^{18}F]-fluoro-2-deoxy-d-lucose (FDG) had been used to demonstrate decreased frontal cerebral metabolism in adults with ADHD (Zametkin et al., 1990) although inconsistent results in adolescents (Zametkin et al., 1993; Ernst et al., 1994; Ernst &. Zametkin, 1995) led the authors to explore other techniques in ADHD (Ernst et al. 1998). Other investigators have measured local cerebral blood flow, which is closely linked to neuronal activity and tissue metabolism, with a variety of techniques including ^{133}Xenon inhalation and single-photon emission tomography. Decreased blood flow has been found in ADHD subjects in the striatum (Lou et al., 1990) and in prefrontal regions (Amen & Paldi, 1993). However, these results must be interpreted cautiously because ethical constraints make it difficult to obtain truly independent observations from normal control children. A more promising technique is blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI), which obviates the need to use ionizing radiation.

The BOLD fMRI technique was used in a study of 10 boys with ADHD and 6 controls, all of whom were scanned on and off methylphenidate while they performed Go No-Go tasks (Vaidya et al., 1998). The authors extended to methylphenidate the observation that stimulants improve performance in normal children as they do in patients with ADHD (Rapoport et al., 1978). In caudate and putamen, Vaidya and colleagues found a striking group difference. In the task with the faster stimulus presentation rate, methylphenidate increased the number of activated pixels in caudate and putamen in ADHD subjects, but it had the opposite effect in the controls. In both caudate and putamen, controls activated significantly fewer pixels when scanned while on methylphenidate compared to drug-free scans. Perhaps equally interesting was the finding that patients as well as controls activated significantly larger numbers of pixels in prefrontal cortex on drug. This regional dissociation between prefrontal cortex and striatum is consistent with the

finding that ventral tegmental area dopaminergic neurons, which mostly innervate prefrontal cortex, lack autoreceptors, while nigrostriatal dopamine neurons have abundant numbers of autoreceptors (Meador-Woodruff et al., 1994). Differences in neuronal autoreceptor regulation have been hypothesized to underlie the therapeutic effects of psychostimulants (Castellanos, 1997; Solanto, 1998, 1984), and the pattern of findings in the normal controls fits the prediction that methylphenidate would increase activation in prefrontal neurons by increasing synaptic and extrasynaptic dopamine levels; however, it would have the reverse effect in the striatum by producing a regulatory inhibition of firing. If replicated, these findings suggest that ADHD children differ qualitatively in striatal dopamine regulation and that such a difference may reflect etiological factors. However, before accepting this interpretation, we must note that all the patients had been medicated with methylphenidate until 36 hours prior to their scans. Since the normal controls had by definition never been previously exposed to stimulants, the possibility that these findings reflect medication withdrawal effects must first be excluded in replications and extensions of this work.

Frontal striatal circuits were targeted in another fMRI study using a sample of 7 adolescent boys with ADHD who were unmedicated or medication free for at least one week before scanning and 9 controls (Rubia et al., 1999). Subjects were scanned while performing the Stop Task (Schachar et al., 1995) and a delay task that required synchronization of a motor response to an intermittently appearing visual stimulus. The hyperactive subjects showed less brain activity, predominantly in the right medial frontal cortex during both tasks, and in the right inferior prefrontal cortex and left caudate nucleus during the Stop Task. They concluded, "the right inferior frontal lobe — and its projections to the caudate — has been related to response inhibition…. It thus seems that the brake system of the brain is localized to the right prefrontal lobe, and its underactivation in ADHD seems to be the neural correlate of a less efficient inhibitory motor control" (Rubia et al., 1999) (p. 895).

The principal limitation of fMRI explorations of ADHD is the exquisite sensitivity of the technique to even minimal movement during scanning. Vaidya and colleagues (1998) found that

using a bite-bar was essential in their study of children with ADHD and child controls. Rubia et al. (1999) included only adolescents who were able to remain sufficiently immobile in the scanner. Because physical restlessness decreases with age (Levy, 1980), Bush and colleagues (1999) studied eight adults who had a history of childhood onset and persistence into adulthood of ADHD and eight matched controls using the Counting Stroop during fMRI. The Counting Stroop was used to avoid verbal responses; rather than color words, subjects were shown words that were repeated one to four times per presentation. Subjects were required to press the button corresponding to the number of words, and presenting number words that did not match the number of presented words provided interference (Bush et al., 1998). Although both groups of subjects showed the expected slowing of response times in the interference condition, significant activation of bilateral anterior cingulate was only found in the normal controls. In contrast, ADHD subjects significantly activated right and left inferior frontal gyrus, right and left insula, left caudate, right putamen, right thalamus, and left pulvinar. Thus, the absence of cingulate activation could not be ascribed to a simple failure to activate a neural network, although the authors noted that possible anatomic differences in cingulate volume, and stimulant medication history could have confounded their results. Also, the cognitive task did not result in sufficiently robust activation patterns to allow for single-subject analyses, which is typically a strong point of fMRI studies. Thus, absence of activation could simply reflect greater anatomic variability in the subjects with ADHD. Nevertheless, further exploration with this task and technique in younger subjects is clearly warranted.

3.4 Discussion of the brain studies

This neuropsychological literature proposes a differential right hemisphere contribution in ADHD. Neuroimaging studies have provided convergent evidence to support involvement of frontostriatal circuitry, particularly in the right hemisphere (Castellanos et al., 1994; Casey et al., 1997; Mataro et al., 1997; Rubia et al., 1999). Corresponding hemispheric asymmetries implicating anterior right hemisphere involvement have also been noted in EEG and event-related potential

studies (Oades et al., 1996; Pliszka, Liotti & Woldorff, 2000). These findings provide electrophysiological validation to preceding neurobehaviorally driven hypotheses of developmental right hemisphere dysfunction in ADHD (Voeller & Heilman, 1988; Heilman et al., 1991). In addition, it has been noted that ADHD is commonly associated with the kind of problems in academic achievement, affect perception/regulation and socioemotional cognition that are commonly seen in developmental right hemisphere dysfunction (Weintraub & Mesulam, 1983; Semrud-Clikeman & Hynd, 1990; Brumback & Staton, 1982; Voeller & Heilman, 1988). Several authors have further proposed the existence of an anterior to posterior gradient for subtypes, mechanisms, and higher order cognitive deficits. Inhibition tasks coupled with neuroimaging most clearly implicate dysfunction of anterior right-sided frontostriatal systems. By contrast, other studies examining several aspects of attention and spatial cognition imply subtle disturbances in broader components of the right hemisphere distributed attention regulation system, including right posterior parietal regions. Evidence for this anterior/posterior gradient hypothesis has been mixed (Hynd et al., 1991; Landau et al., 1999; Schaughency et al., 1989; Matazow & Hynd, 1992). Tests of this hypothesis have largely relied on attempts to contrast patterns of performance on "frontal" and "parietal" neuropsychological tasks in ADHD subtypes (i.e., hyperactive/impulsive and inattentive, respectively). However, the validity of this approach is contingent upon the specificity and sensitivity of the measures used to assess anterior and posterior functions of the right hemisphere. Any number of task or subject related factors can compromise the necessary behavioral or neuroanatomic specificity that would allow clear differentiation between groups. Lastly, few studies have implicated temporal lobe function (or central brain regions), so arguably a more appropriate working model might be anterior and posterior *nodes* rather than a *gradient*. A major methodological problem when trying to assess the implications of this evolving literature, regarding either the role of the right brain and/or the question of differential involvement of anterior or posterior nodes, is the diverse spectrum of subjects subsumed in the research studies: ADHD has a varied behavioral profile, as well as mixed genetic and traumatic etiologies (Lou, 1996). Yet sample

characteristics are seldom closely considered in this body of research. Often, subjects have not been well described in detail beyond labeling them ADHD, or studies have been limited to only hyperactive subjects. Family history is seldom if ever considered. Common comorbid conditions like learning disability, Conduct Disorder, or TS are either included or alternatively are not mentioned. In future studies, it will be increasingly important to reduce the heterogeneity by incorporating information regarding typology or comorbidity in a more systematic and refined manner.

3.5 Theories of the neuropsychological mechanisms responsible for ADHD

An overview of the broadly defined neuropsychological literature reveals that research has focused on three theoretical mechanisms for the behavioral symptoms of poorly controlled attention in ADHD: response disinhibition, executive dyscontrol, and attentional disinhibition (failure of selective attention). While these categories are not mutually exclusive, the tests used are typically characterized as belonging to one of these categories. For example, response inhibition is considered an executive function, yet neuropsychological tests of executive functioning define the cognitive load as that of decision-making, as an aspect of organization of perception or memory, as estimates of timing, of motor control, or of selective attention often involving inhibitory mechanisms of different types. Thus, we separate response inhibition and selective attention into their own categories owing to the more in-depth attention given to these constructs.

3.5.1 Response Dysinhibition

The majority of studies have investigated the hypothesis that the symptoms are manifestations of response dysinhibition, usually measured as errors of commission or false alarm errors. Often the tests used are based on both response and attentional inhibition, thus confounding the two issues. The most commonly given test is the continuous performance test (CPT), and it has consistently revealed deficits in groups of children and adults with ADHD (Epstein et al., 1998;

Walker et al., 2000), although its selectivity for ADHD is considered weak in discriminant analysis. In the more common, visual modality version of this test, letters or numbers appear on a computer screen, usually individually, at the rate of about 1 per second. The child must respond selectively to stimuli that are targets. Targets may be simple (e.g., respond to the letter "A") or more complex (respond to the "A" when it comes after an "X"). The task can be made more complex by including stimuli that are distracting by being similar to the targets, or by increasing the memory search required in the task. Children usually make errors of commission, which means they are either responding to the wrong stimulus because their responses come too late, or they make an error due to impulsivity and respond to the wrong stimulus (Halperin et al., 1988). While this finding is common, it does not tell us anything new about ADHD, in that it only reveals that the individuals are impulsive, slow, and have poor control of their responses. It doesn't reveal the cognitive mechanism underlying the inattention or response dysinhibition.

A classic version of response inhibition is the stop-signal task, in which subjects engage in a primary task, and occasionally are presented with a signal that tells them to stop their response to the primary task (Castellanos et al., 2000). Oosterlaan, Logan, and Sergeant (1998) found evidence of poor response inhibition in a meta-analysis of several auditory stop-signal studies of children with ADHD. A consistent deficit in response inhibition was found; however, the deficit did not distinguish ADHD children from a control group of children with conduct disorders. The lack of difference might be due to overlap in sampling methods, as not all of the studies used in the meta-analysis controlled for comorbid psychiatric disorders. Oosterlaan and Sergeant (1998) also tested the hypothesis that a response inhibition problem may be a function of an underlying motivational deficit. They implemented response reward and response cost contingencies in a stop-signal task, and found that the ADHD children still displayed response inhibition deficits. Quay (1997) reviewed the performances of children with ADHD on stop-signal tasks, and found that they made more errors than did normal control children, specifically errors of commission. As errors of

commission are more specifically errors of response, than errors of omission which are more specifically selective attention errors, this finding is indicative of a response inhibition impairment.

3.5.2 Executive Dysfunction

The search for an explanation of ADHD related to executive dysfunction is based on the similarity of some of the disturbed behaviors in clinical populations of known frontal lobe-injured patients with individuals who have ADHD, specifically the problems of self-regulation and behavioral inhibition. The executive dysfunction hypothesis also gains support from the findings of smaller or inactivated frontal systems in neuroimaging studies. However, the validity of the executive function mechanism is not well established, in part because impaired executive functions are not specific to diseases of the frontal lobes. Usually, the executive function mechanism for ADHD is invoked in studies in which a variety of tests that have been associated to varying degrees to the frontal lobe (e.g., verbal fluency, planning, response inhibition, memory) are used together in the hope that the "executive battery" will increase the sensitivity and specificity in discriminating individuals with ADHD from normal controls. Even proponents of the executive explanation for ADHD are critical of the sufficiency of the executive mechanism to predict ADHD, noting that the sensitivity and specificity of a battery of "frontal lobe" tests, including several that are considered measures of executive functioning, was mediocre at best in identifying children with ADHD (Grodzinsky & Barkley, 1999).

3.5.3 Selective Attention and Attentional Dyisinhibition

Selective attention is the discrimination of relevant from irrelevant information in memory, requiring automatic processing (Schneider & Shiffrin 1977; Shiffrin & Schneider, 1977). It is automatic in that it is an early form of cognitive evaluation that is not dependent on conscious intention to compare or discriminate targets. Attentional inhibition follows in order to inhibit the irrelevant information from further processing. A consistent and dysfunctional behavior in both

children and adults is that of switching one's attention too quickly resulting in failure to attend to relevant stimuli, so that tasks remain unfinished. Performance on Stroop interference trials are typically given as evidence of a failure to control the interference from irrelevant, nontarget stimuli (e.g., see Carter, Krener, Chaderjian, et al., 1995). Thus, children, though not adults, with ADHD are consistently slower to name colors when stimuli are color-incongruent words, indicating that they are less able to inhibit the color-incongruent stimuli. While the Stroop studies are provocative, they are not a direct test of attention inhibition, as there is no measure of actual reaction time. Carter and colleagues (1995), using carefully controlled test conditions and sampling procedures, required children to focus on a central stimulus that indicates in which direction the target will appear (Posner's paradigm), and then measured their response times to detect the targets. Sometimes these indicating cues were valid and sometimes invalid (pointed to the incorrect direction). In this study, endogenous cues were used, to keep visual fixation at the fovea, thus eliminating problems of returning attention from cues that occur in the periphery. Children with ADHD showed no difference from controls in reaction time when the cues were valid. However, when the cues were invalid, the expected increased reaction time did not occur in the children with ADHD for those targets that occurred in the left visual field only, a finding that is consistent with previous work (Swanson, Posner, Potkin, et al., 1991). Thus, they were responding "too quickly" to invalidly cued targets in the left visual field, whereas there is usually an advantage for targets appearing in the right visual field in most right-hand-dominant children. This effect was interpreted as failure of visuospatial selective attentional mechanisms of the right hemisphere, based on a proposition that cueing of attention to one visual field requires inhibition of attention to the contralateral visual field. This would predict faster activation of attention for validly cued targets, and slower activation for invalidly cued targets because the "correct" field was inhibited by the invalid cue. However, the abnormally quick response of children with ADHD to the invalid cues to targets in the left visual field, suggests defective inhibition of attention by the right hemisphere.

3.5.4 Memory impairments

Further conceptualizations of the core deficit of ADHD focused on deficits in executive processing which results from a breakdown in the executive control of attention and goal directed behaviors (Schachar, 1991). Higher level of attentional control is inherent in the ability to "construct, execute, choose, maintain operational strategies and inhibit strategies which become inappropriate" (Schachar & Logan, 1990, p. 710). Theoretical frameworks which permit a closer examination of the precise nature of executive processing include the Working Memory model (Baddeley, 1986). This model was proposed to replace the notion of a single flexible short-term memory system (Baddeley, 1992). Instead it includes a number of components that are responsible for different forms of processing and temporary storage of information. These include a modality free, controlling central executive aided by subsidiary slave systems, namely the phonological loop and the visuo-spatial sketch-pad (Baddeley, 1992).

Phonological loop is known to be impaired in reading disabled children (RD) (see Jorm, 1983, for a review), and children with ADHD are found to be impaired in tasks tapping the central executive (Barkley, 1997, Roodenrys et al., 2001). For clinical and theoretical purposes, it is important to establish whether children with RD, ADHD or with comorbidity are impaired in working memory tasks and in the use of memory strategies. The majority of evidence regarding phonological loop functioning in ADHD and RD children supports the assertion that ADHD children, in comparison with RD children, are not impaired in phonological loop functioning (Korman & Pesonen, 1994).

In order to find the core memory deficit in children with ADHD most of the researches focused their analysis on the functioning of the central executive system of the working memory (Baddeley, 1986) and on the use of learning strategies. The hypothesis is that children with ADHD have poorer memory performance due their executive control impairment and their inability to efficiently apply learning strategies. The results of researches with ADHD children on memory tasks are controversial: some studies found significant different between ADHD and controls

(Roodenrys, Koloski & Grainer, 2001; Cornoldi, Marzocchi, Belotti, Caroli, De Meo & Braga, 2001) but some did not (Stevens, Quitter, Zuckerman & Moore, 2002; Dewey, Kaplan, Crawford & Fisher, 1998; Kuntsi, Oosterlaan & Stevenson, 2001).

Among the studies which did not find any working memory difference between ADHD and controls, Stevens et al. (2002) compared a group of ADHD to normal controls on a memory task which presented colored series of digits (from two to nine). The task presented two conditions: 1) naming colors and then recalling digits (working memory), 2) only recalling digits (short-term memory). The group of ADHD children performed significantly poorer on the short-term condition, but not on the working memory one. Moreover, Dewey et al (1998) compared children with ADHD or RD to Normal Controls administering the WRAML battery finding that ADHD children were not different from normal controls, whereas children with RD were significantly poorer than controls on verbal memory subtests and on the learning index. More specifically, Kuntsi et al (2001) used a sentence span task (Daneman & Carpenter, 1980) to assess the central executive in a group of children with ADHD. In the sentence span task the tester reads sentences out to the child who has to supply the missing word for each sentence. At the end of each set, the child is asked to repeat all the words that he had supplied, in the correct order. In this task the ADHD group was impaired, but, when IQ was controlled, the difference between ADHD and Controls was no longer significant.

Other studies on working memory, found significant difference between ADHD and controls: Roodenrys et al (2001) analyzed the working memory functioning in children with ADHD or RD on measures tapping the phonological loop and the central executive according to Baddeley's (1996) model. Both ADHD and RD were impaired in phonological loop measures (digits and words spans), but in particular children with ADHD were more impaired than RD and Controls in tasks that assessed the central executive (PASAT, Memory updating, and Random generation tasks). A task similar Sentence Span test was proposed by Cornoldi, Marzocchi, Belotti, Caroli, De Meo & Braga (2001) in which a series of lists of four words (the series increased from two to five) was administered to the child. The subject had to tap on the table when an animal noun was presented;

the child had also to remember the last words of the lists. At the end of each series the child had to recall the last words of the lists in the exact order they were presented. Children with ADHD recalled fewer correct sequences of last words and produced more errors due to interferences because they recalled words which were not in the last position of the list.

As far as the use of memory strategies in ADHD children is concerned some researches found positive results (O'Neill & Douglas, 1991; Douglas & Benezra, 1990; Kramer, Knee & Delis, 2000; Sechi, Corcelli & Levi, 1999; Cornoldi, Barbieri, Gaiani & Zocchi, 1999) but some not (Mahone, Koth Cutting, Singer & Denckla, 2001).

O'Neill and Douglas (1991) presented ADHD, RD and Controls with a story on two learning conditions: immediate recall and study recall. In both immediate and story recall conditions only children with RD performed significantly more poorly than Controls. However, children with ADHD used less efficient strategies and spent less time than controls in the story recall condition but their performance, although a bit inferior than those of controls, was not statistically different. Douglas & Benezra (1990) presented ADHD, RD and Controls with a five sets of supra-span lists of 12 items. RD recalled fewer words than controls, and ADHD children's performance although inferior was not significantly poorer than performance of control children. In a paired associate learning task (the pairs included semantically related or not related words) children with ADHD were impaired when the words were not semantically related, whereas RD children performed significantly poorer than controls in terms of total pairs recalled. Douglas & Benezra (1990) concluded that children with ADHD were particularly impaired in learning material that requires organized, deliberate rehearsal strategies, sustained strategic effort and careful consideration of response alternatives. Sechi et al. (1999) analyzed memory performance of children with RD and ADHD+RD on four tasks: immediate memory, learning of supra-span unrelated items, learning of supra-span related items, and story recall. On the immediate memory tasks the three groups did not significantly differ each other; on the learning supra-span tasks the ADHD+RD were more impaired than control children, in particular with unrelated items, where more elaborated memory strategies

were required. On the story recall task the children with RD were more impaired than ADHD+RD and normal controls. Cornoldi, Barbieri, Gaiani and Zocchi (1999) administered to ADHD and control children a 4 trial-free recall task of categorizable an partially repeated material (pictures). ADHD subjects recalled fewer correct words but made more interference errors. The differences between ADHD and controls did not disappear even when they were informed about the use of appropriate memory strategy. The ADHD children performed similar to controls only when they were informed and assisted on the use of strategies. The authors (Cornoldi et al 1999) concluded that children with ADHD were able to recognize efficient memory strategies (metacognitive knowledge) but they were impaired in the correct application of memory strategies (executive process). However, not all studies consistently reported a deficient use of memory strategies in ADHD children: for instance, Mahone et al. (2001) using the California Verbal Learning Test for Children (CVLTC) found that subjects with ADHD were not impaired in the application of semantic clustering, and they did not recall fewer items than normal controls; and they made more intrusion errors.

3.6 Cognitive Neuropsychology of ADHD subtypes

Although more work is needed to understand the neuropsychological correlates of the ADHD subtypes, we do know a fair amount about the neuropsychological correlates of ADHD as a global category. Tests that tap neurocognitive domains such as vigilance, sustained attention, and executive function (EF) have been useful in distinguishing those with ADHD from controls. Children with ADHD fairly consistently exhibit poorer performance on measures of EF, vigilance, and perceptual speed, but usually perform within normal limits on a variety of verbal or spatial measures (Barkley, 1997; Pennington & Ozonoff, 1996). Within the EF domain, tests of motor inhibition such as Continuous Performance Tasks and the Stop Task are especially sensitive measures of ADHD (Pennington & Ozonoff, 1996). In a meta-analysis of studies using the Stop Task (Oosterlaan & Sergeant, 1998), consistent deficits were demonstrated in groups with ADHD,

providing evidence that children with ADHD are impaired in their ability to inhibit. Moreover, this deficit has not been found to be explainable by IQ, comorbid disorders, or reading disability, suggesting that it may be specific to ADHD (Nigg, 1999; Oosterlaan & Sergeant, 1998). Studies of neuropsychological function in ADHD that have used previous subtype distinctions have obtained mixed results. The third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-III*; APA, 1980) defined two subtypes of ADHD; ADD with hyperactivity and ADD without hyperactivity. Arguably, these two previous subtypes are somewhat comparable to the current ADHD-Combined and ADHD-Hyperactive subtypes, respectively (McBurnett et al., 1999). A review by Carlson (1986) demonstrated that children with the *DSM-III* subtypes of ADD with hyperactivity and ADD without hyperactivity both showed deficits on neuropsychological tests compared to controls, and there were few differences between these subtypes. Other studies using clinical samples have also found few differences between these groups on cognitive measures (Hynd et al., 1989; Schaughency, Lahey, Hynd, Stone & Piacentini, 1989). In contrast, in a school-based study, Sergeant and Scholten (1985) found children with ADD with hyperactivity to be significantly slower and less accurate than controls, whereas children without hyperactivity differed from controls only in showing a slower search rate. Barkley, DuPaul, and McMurray (1990) also found significant differences between these groups on cognitive measures using a clinical sample. Children without hyperactivity were found to have deficits in timed perceptual-motor tasks, but did not exhibit deficits in impulsivity or sustained attention on a vigilance task. Those with hyperactivity exhibited no deficits on the timed perceptual-motor tasks, but exhibited impulsive responding and difficulty in sustained attention. These findings by Barkley et al. (1990) and Sergeant and Scholten (1985) suggest that differential deficits in processing speed and inhibition may discriminate between the previous *DSM-III* subtypes. To date, there have been relatively few studies regarding the neuropsychological performance of children with the current *DSM-IV* subtypes, and those that have been conducted have obtained inconsistent results. Houghton et al. (1999) found that although ADHD-Hyperactive and ADHD-Combined children were significantly

different from controls on measures of inhibition, planning, and set-shifting, the two subtypes were not significantly different from one another (although only the combined type differed from controls in perseveration and response inhibition). In contrast, utilizing a combined clinical and community sample, Nigg, Blaskey, Huang-Pollack, and Rappley (2001) found that boys with ADHD-Combined exhibited deficits in behavioral inhibition relative to boys with ADHD-Hyperactivity. Girls in both of these subtypes, however, had similarly deficits on the inhibition measure. Both subtypes also exhibited deficits in processing speed in this study. On the other hand, Chhabildas et al. (2001) did not find a double dissociation between subtypes with Inattention or Hyperactive symptoms using tasks measuring inhibition and attention skills: children with Inattention symptoms were impaired on both attentional and inhibitory measures whereas children with mostly Hyperactive symptoms were only impaired on inhibitory tasks.

Finally, in a clinic-based study, Klorman et al. (1999) found that children with ADHD-C (Combined) achieved fewer correct solutions and made more rule violations than children without ADHD on the Tower of Hanoi, a measure of planning, whereas children with ADHD-IA (Inattention) were not significantly different from the comparison sample. Clearly, more research is needed to determine whether the *DSM-IV* subtypes of ADHD are associated with differential neuropsychological impairments.

Chapter 4

Executive Function impairments in children with ADHD and Learning Disorder (LD)

4.1 ADHD and Learning Disability: which comes first?

Before reviewing the literature on ADHD and LD it is necessary to clarify that in the current literature competing hypothesis to explain reading disorder are present: the phonological deficit (Bradely & Bryant, 1978); the magnocellular theory (Livingstone, Rosen, Drislan & Galaburda, 1991), the temporal processing deficit (Tallal, 1980) and the cerebellar theory (Nicholson & Fawcett, 1995). (For a comparison of the four theories see White, Milne, Rosen, Hansen, Swettenham et al., 2006). However, in the present work this hyphotesis will not be deeply discussed since it is not the aim of this work and the material proposed to children do not allow to make inferences on the four theory on developmental dyslexia.

Children diagnosed with hyperactivity often show poor educational attainments and children with specific learning disabilities show an increased risk of hyperactivity and other behavioural problems (Cantwell & Baker, 1991; Faraone et al., 1993; Samuelsson, Lundberg & Herkner, 2004; Semrud-Clikeman et al., 1992). The term Learning Disorder (LD) used in this context refers to a specific learning deficit that could affect reading, spelling or calculation skills. Although the extent of the overlap has inevitably varied from study to study depending on the definition of specific learning disabilities and the criteria used in identifying hyperactivity (Semrud-Clikeman et al., 1992), the association between them is not really in doubt. The nature of the association, however, remains uncertain (Hinshaw, 1994). Several possible causal models that might account for the association may be identified (Caron & Rutter, 1991; Hinshaw, 1992; McGee & Share, 1988; Stevenson, Pennington, Gilger, DeFries & Gillis, 1993). First, hyperactivity might lead to specific learning disabilities (Keough, 1971). Attentional problems and impulsivity might interfere with learning by reducing stimulus inspection or information processing time, the cumulative impact of which may be poor acquisition of new information and failure to master basic skills such as reading.

Second, reading difficulties might lead to behaviour problems such as hyperactivity (Cunningham & Barkley, 1978). Reading difficulties are likely to interfere with the child's ability to follow many, if not most, aspects of the school curriculum. In the classroom, the child is less likely to pay attention to lessons and more likely to engage in behaviours that are almost by definition "off-task" and often disruptive. The child's disruptive off-task behaviours may become fuelled by stigma, frustration, low self-esteem, or resentment at not being able to keep up with the rest of the class, increasing the likelihood of these behaviours occurring in other situations. Third, both reading problems and hyperactivity might be due to some other cause common to both, such as social disadvantage, genetic factors, or neurological impairment. Fourth, reading difficulties and hyperactivity might have different causes, but the causal factors might themselves be correlated. For example, poor teaching skills (resulting in a child having reading difficulties) may be correlated with ineffectual classroom management practices (resulting in a child appearing hyperactive). Alternatively, separate but correlated genetic factors might lead independently to the two conditions (ADHD and RD). Several authors have shown that children with the combination ADHD and reading difficulties resemble children with reading difficulties alone in showing deficits on verbal tests, particularly phonological processing tasks (Felton, Woods, Brown, Campbell, & Harter, 1987; Korkman & Pesonen, 1994; McGee, Williams, Moffitt, & Anderson, 1989; Pennington, Grossier & Welsh, 1993; Shaywitz et al., 1995). Whether or not the pattern of deficits observed in the ADHD-reading difficulties group differs from that in the group with ADHD alone is more uncertain. Pennington et al. (1993) found that, unlike the ADHD-reading difficulties group, children with ADHD alone were impaired on executive function tasks, and argued that since the two reading difficulties groups show similar underlying cognitive deficits, the ADHD symptoms of the ADHD-reading difficulties group arise as a consequence of their reading difficulties. However, other studies have provided evidence of *both* language and executive function deficits in the comorbid group (Korkman & Pesonen, 1994; Purvis & Tannock, 1997), and although these latter findings do not conflict with the idea that features of ADHD develop as a consequence of reading

difficulties, they clearly open the door to several other possibilities. Longitudinal investigations are potentially more useful than cross-sectional studies in clarifying issues of sequence and hence in drawing inferences about causation. Several follow-up studies of school entrants suggest that children who are later identified as showing reading difficulties often showed behavioural problems at the time when they started school (Chazan, 1983; McGee, Williams, Share, Anderson, & Silva, 1986; McMichael, 1979; Stott, 1981). Although these findings are consistent with the possibility that behavioural problems lead to academic difficulties (Stott, 1981), the finding that even at the time of school entry behavioural and emotional difficulties are associated with poor reading readiness scores (McMichael, 1979) and weaknesses in skills such as writing and drawing (Chazan, 1983) suggests that this conclusion may be unwarranted. These studies underline the importance of taking into account the frequent co-occurrence of behaviour problems and reading disability when examining the longitudinal impact of behaviour problems on subsequent reading progress and of reading disability on behavioural outcome. Among studies that have done so, evidence consistent with the hypothesis that features of hyperactivity develop in reaction to academic underachievement has come primarily from the Dunedin Longitudinal Study. McGee and colleagues (1986; McGee, Share, Moffitt, Williams & Silva, 1988) observed an increase in the severity of behaviour problems, particularly teacher-rated hyperactivity, in reading-disabled boys over the early school years. Pisecco, Baker, Silva, and Brooke (1996) have extended these findings by presenting data on parent and teacher behaviour ratings up to adolescence in four groups of boys defined by the presence or absence of ADHD and reading disability. Whereas parent ratings showed few behavioural differences between the two reading disabled groups and their control groups, teacher ratings showed elevated levels of hyperactive and antisocial behaviour in the group with reading disability alone. These findings are consistent with the possibility that reading difficulties may in some children lead to the expression or exacerbation of ADHD and antisocial behaviours at school. Nevertheless, this conclusion is based essentially on the consistent pattern of cross-sectional findings in different age groups; although the pattern of longitudinal findings showed an increase in

teacher-rated overactivity until middle childhood, this pattern was not specific to children with reading disabilities and the levels appeared to decline in adolescence (Chadwick, Taylor, Taylor, Heptinstall, & Danckaerts, 1999). Other longitudinal studies of shorter duration have failed to find evidence of an effect of reading disability on subsequent activity or attention levels (Smart, Sanson & Prior, 1996) Finally, Maughan, Pickles, Hagell, Rutter, and Yule (1996) found that the increased risk of teacher-rated overactivity they had observed in 10-years old with reading difficulties was no longer present when the children were re-examined at the age of 14. Most follow-up studies of children with clinically diagnosed hyperactivity indicate that not only does their hyperactivity persist, albeit often in an attenuated form, but so too does their increased risk of academic underachievement (Fischer, Barkley, Edelbrock, & Smallish, 1990; Lambert, Hartsough, Sassone & Sandoval, 1987; Piacentini, Mannuzza, & Klein, 1987; Willcutt et al. 2005). Furthermore, among studies of non-clinical samples, Fergusson and Horwood (1992) examined data from the Christchurch Health and Development Study to investigate the reciprocal relationships between reading ability on the one hand and combined parent and teacher ratings of overactivity and inattention on the other in a cohort of children who were studied at 10 and 12 years of age. There was little evidence to support the idea that reading ability influences hyperactivity, but the findings were consistent with the possibility of modest but statistically significant effects of hyperactivity on reading ability.

Subsequent studies by the same authors extended this finding by showing that hyperactivity in middle childhood is associated with scholastic performance at 18 years independently of any effects of potentially confounding factors such as conduct problems, socioeconomic disadvantage, or IQ (Fergusson et al., 1993; Fergusson, Lynskey & Horwood, 1997). Maughan et al. (1994), however, found no differential effects of teacher-rated overactivity (or antisocial behaviour) on reading progress between the ages of 10 and 14 years. A number of other studies have produced evidence to support the view that hyperactivity and other behavioural problems develop in reaction to reading difficulties, but little of this evidence is longitudinal in nature.

4.1 The nature of the comorbidity of ADHD and LD

Shaywitz and Shaywitz (1991) noted that the diagnosis of ADHD is established by a history of inattention, impulsivity and hyperactivity, whereas the diagnosis of LD is made on the basis of a discrepancy among tests of ability (e.g., IQ) and performance on tests of achievement. They concluded that naming and linguistic fluency deficits reflect reading disability, whereas verbal learning and memory deficits are linked to attention disorder. They also proposed that ADHD and LD are distinct disorders, though they occur together in a large number of children. Given that the definitions for ADHD and LD are based on independent assessment methods, investigation of the effect of the comorbidity of LD would avoid the assessment confusion found between ADHD and conduct disorder.

However, despite this benefit and the awareness of the relationship between ADHD and LD, Jensen, Martin, and Cantwell (1997) noted that evidence of the comorbidity between ADHD and LD accumulated so far remains inconclusive. They also proposed that measures to assess the different aspects of attention and working memory are needed to distinguish subtypes of ADHD by comorbidity. Thus far, few researchers have addressed the unique difficulties in components of executive functioning (i.e., attention and response inhibition) experienced by children with ADHD when LD is also present. It is probable that ADHD and LD are associated with deficits in different executive components. In fact, these possibilities are supported by previous research. First, attentional deficits associated with LD are suggested in previous studies. For example, Cermak and his colleagues (Cermak, Goldberg, Cermak, & Drake, 1980) have documented the information processing deficits in children with LDs by utilizing a series of information-processing tasks in the laboratory. They found that the rate and level at which children with LDs process information are below the standards set by normal controls. There is also substantial evidence that indicates that LD is a reflection of central nervous system disturbance (for a review see Hynd, Marshall, & Gonzalaz, 1991). However, the attentional deficits associated with LD suggested in these studies are not

specific. Swanson (1993) conducted a study on specific attentional deficit associated with LDs. Verbal and visuospatial working memory measures were used in the study to examine the effect of LD. Most of the results in the literature indicate that children with LDs suffer generalized working-memory deficits, possibly due to storage constraints in the executive system (Gathercole & Pickering, 2000). However, this topic is discussed in the literature because other reserarchers found no association between working memory impairment and LD (Jarvis & Gathercole, 2003). Therefore, research on ADHD that has not taken the effect of LD into consideration may have wrongly attributed the associated deficit of LD to ADHD. Prior to the review by Biederman et al. (1991), few researchers had undertaken any systematic examination of ADHD children with and without LDs. The few studies that undertook this effort failed to find differences between comorbid and noncomorbid groups. In fact, the distinction between ADHD and LD has been called into question by earlier studies (Halperin, Gittelman, Klein, & Rudel, 1984; Prior & Sanson, 1986). Prior and Sanson (1986) argued that there is little evidence from past research to support the tenet that ADHD and LD can be differentiated on the basis of attentional deficits. However, there are studies that show that ADHD and LD are related to different specific attentional deficits. In a study utilizing an information processing framework (Van der Meere, Baal, & Sergeant, 1989), results indicate that LD is associated with particular difficulty in the central stages of processing (i.e., memory and decision, indicative of a divided attentional deficit), whereas ADHD is associated with difficulty in motor response. Thus, both groups exhibited slower RT when compared to the control group, but due to different underlying deficits. In another study, it was found that ADHD children with and without reading disability can be differentiated from the normal controls on laboratory measures of sustained attention and impulse control (Dykman & Ackerman, 1991). As children with reading disability show poorer performance than those without reading disability, these researchers advocate the importance of assessing LD in ADHD. Most of the experimental research until recently has ignored the coexistence of LD in ADHD. For example, in a study aiming to differentiate children with ADHD from normal controls by using neuropsychological and

behavioral assessment, coexistence of other childhood pathologies were not taken into consideration (Pieneda, Ardila, & Rosselli, 1999). Thus, even though findings indicate that children with ADHD can be reliably discriminated from normal controls in test measures, it is not certain if the difference between the ADHD and control groups was due to ADHD or other comorbidities. As suggested by Hinshaw and Park (1999), ADHD children with or without comorbid psychopathology (e.g., LD), may differ radically with respect to causal factors, correlates, course, and treatment response. Thus, research that screens for comorbidity of LD is important with respect to the understanding of ADHD. Through careful screening of ADHD children for LD, this study attempts to differentiate the specific deficits associated with ADHD and the comorbidity of LD in various components of executive functioning. These findings suggest that ADHD may be associated with deficits in speed of processing for verbal response and sustained attention. The comorbidity of LD was found to be specifically associated with the deficits in selective attention and attentional capacity. The results are discussed in terms of their implications on the specific deficits associated with ADHD and the theoretical models for ADHD. Alternative explanations and limitations of the study are also discussed.

4.3 Is ADHD associated with Executive Functioning impairments?

As introduced in paragraph 3.5.2, a number of the behavioral manifestations of ADHD parallels those behaviors associated with executive processing deficits. Children with ADHD have difficulty with inhibitory control (Schachar & Logan, 1990), planning and organization (Grodzinsky & Diamond, 1992), and self-regulation (Barkley, 1990), which has led to the proposal that the primary impairment of ADHD is one of executive processing. The examination of executive processing in ADHD children has been sporadic with most evidence accumulated post hoc from studies employing neuropsychological tests most commonly used to assess frontal lobe injuries in adults (Barkley, Grodzinsky, & Du Paul, 1992). Results from studies using these tasks have been controversial; however, in general, an executive function deficit in ADHD children has been

indicated. Boucugnani and Jones (1989) found that ADHD children were significantly impaired on the Wisconsin Card Sorting Test (WCST), the Trail-Making Test–B, and the Stroop task, which was taken to indicate problems with self-directed attention, inhibitory capacity, and perseveration. Grodzinsky and Diamond (1992) found that ADHD boys were impaired on tasks measuring impulsivity and planning, whereas Barkley et al. (1992), in a review of 22 neuropsychological studies of ADHD, found that most studies demonstrated an impairment in cognitive flexibility as measured by the WCST and also a difficulty with inhibitory control as measured by the Continuous Performance Test. Barkley et al. concluded from the pattern of findings that ADHD was best characterized as a disinhibition disorder. Further support for the executive dysfunction hypothesis came from a study by Weyandt and Willis (1994), who found that a battery of executive function tasks, including the Matching Familiar Figures Test, Tower of Hanoi, and mazes, were able to significantly discriminate ADHD children from controls. Furthermore, non-executive function tasks of vocabulary were unable to differentiate the two groups, which supported the discriminant validity of the executive function tasks (Weyandt & Willis, 1994). These studies provide strong evidence for the implication of an executive processing deficit in ADHD children. However, one criticism of the executive processing research to date is that there has been little attempt to isolate the specific difficulties that ADHD children display on these tasks. Many executive function tasks tap multiple processes and may also require non-executive processes for successful performance (Pennington & Ozonoff, 1996). This makes interpretation of deficits on these tasks ambiguous because the individual component processes responsible for the impaired performance are difficult to identify. Another criticism of many executive function tasks is that they are not specified theoretically (Pennington & Ozonoff, 1996). Most studies examining executive functions in ADHD children lack a clear theoretical framework within which cognitive processes and deficits in these processes can be operationalized and specific outcomes predicted.

4.4 Limitations of existing measures

According to extensive reviews of studies that examined the aetiology of ADHD, the most widely accepted interpretation of the present neurophysiological findings regarding ADHD is that fronto-striatal networks may be involved (Castellanos, 1999; Tannock, 1998). However, such evidence has to be accepted with caution, as there are a number of limitations in neurophysiological studies for ADHD (e.g., small sample size, participant selection, and disregard of comorbidity). Studies based on interpretation of performance in tests that are purported to measure executive functions have also yielded inconsistent results. As anticipated in the previous paragraph and reported by Barkley (1992), the Wisconsin Card Sorting Test (WCST; Berg, 1948; Grant & Berg, 1948) is one of the most common clinical tests for examining switching attention, an important component of executive function. In some studies using WCST to assess switching attention and cognitive flexibility of ADHD children, ADHD was found to be impaired (Boucagnani & Jones, 1989; Chelune, Ferguson, Koon, & Dickey, 1986; Gorenstein, Mammato, & Sandy, 1989; Grodzinsky & Diamond, 1992; Johnson, 1991; Loge, Staton, & Beatty, 1990). However, negative findings have also been documented in other studies (Barkley, Grodzinsky, & DuPaul, 1992; Reader, Harris, Scherholz, & Denckla, 1994). As commented by Mountain and Snow (1993), who reviewed the literature on WCST, it is essential to note that interpretation of performance on such a test, which is purported to measure executive functions, has to be cautious. A variety of processes and brain structures are responsible for performance on this test. Thus, WSCT is not able to specify the nature of any underlying specific attentional deficit in ADHD.

The Go/No-Go test has also been applied to evaluate the inhibitory component of executive functions for ADHD children. In one of the studies, ADHD children were found to make more commission and omission errors than controls. They also committed more multiple omission errors (up to three) than controls (Trommer, Hoeppner, Lorber, & Armstrong, 1988). The finding that ADHD children make more commission and omission errors than controls were also replicated by other studies (Shue & Douglas, 1992). However, the reliance of the Go/No-Go test to assess

inhibitory functions has a number of limitations. In some of the studies (e.g., Shue & Douglas, 1992; Trommer et al., 1988), the measures derived from the test only include commission and omission errors, and reaction time (RT) is not measured. A participant's RT to the primary task may become a significant confounding factor that affects the probability of committing such errors. Moreover, only two blocks of 10 trials: five with go signals (i.e., one tap) and five with a no-go signal (two taps) were used in a study using the test (Trommer, Hoeppner, & Zecker, 1991). The interval between taps for the no-go stimulus was fixed at one single interval (i.e., 250 ms). Thus, participants may adopt the strategy of delaying their response in order to wait for the stop signal. These confounding factors were controlled in studies utilizing the stop signal paradigm (Logan & Cowan, 1984; Logan, Cowan, & Davis, 1984), which represents a more sophisticated experimental paradigm for evaluating response inhibition for ADHD children. However, the tasks are often characterized by lack of sufficient norms, especially for children.

The Stroop Color and Word test (Golden, 1987) has been utilized to measure selective attention associated with ADHD. According to a review, five out of six studies that used the Stroop test were able to distinguish ADHD participants from control participants by using the Stroop interference measure (Barkley et al., 1992). Two other studies (Leung & Connolly, 1996; Pennington, Grossier, & Welsh, 1993) also reported a significant difference in the Stroop interference measure between ADHD and control children. However, Seidman, Biederman, Faraone, Weber, and Oullette (1997) reported that the critical Stroop interference score failed to differentiate ADHD children when scores were adjusted for confounding factors such as socioeconomic status, family history, and comorbidity. In summary, assessment measures for general executive functioning (e.g., the WCST and Go/No-Go test) can be multidetermined, so that a single score or general performance on a task is related to the functioning of a number of cognitive domains. Thus, utilization of tests that enabled component analysis is essential in the investigation of the specific deficit in executive functioning for ADHD. Also, the utilization of specific measurements that eliminate the effect caused by difference in lower level abilities (e.g.,

speed of responding) is required. It is also important to adjust the effect related to confounding factors, such as socioeconomic status and comorbidity.

Traditional EF measures usually comprise a single, explicit problem, where the goal is provided by the examiner and trial length is very short. In other words, self-regulation is not demanded of the examinee, and decisions as to task goal, strategies to employ, and whether ongoing behavior needs modification are not necessary. Shallice and Burgess (1991) argued that a valid test of EFs must be a quantifiable analogue of the open-ended, problem-solving situations in everyday life where, although one's general intellectual abilities may be intact, the ability to integrate these skills to use them to organize, monitor, and regulate behavior in carrying out real-life tasks is impaired. Deliberate attentional resources are required to generate explicit intentions or goals and to ensure that ongoing behavior complies with plans made at some earlier time and with rules of behavior or social norms that are not currently salient. In highly structured situations where rules are explicit, and consequences are short-term and perceived by the child as directly related to inappropriate or rule-breaking behavior, hyperactive children can be calm and attentive (Draeger, Prior, & Sanson, 1986). In contrast, an everyday situation in which the child with ADHD has difficulties, for example, is when waiting his/her turn, whether during free play, conversation, or in loosely structured games and classrooms. Where automatic behavior needs to be resisted and a new behavior sequence planned and monitored, parents, clinicians, and researchers report that ADHD behavior is most likely to be seen (Campbell, Pierce, March, Ewing, & Szumowski, 1994; Hinshaw, Simmel, & Heller, 1995). Situations in which children with ADHD appear to have difficulty and which require decision-making and self-monitoring are consistent with the conditions under which the Supervisory Attentional System (SAS) (Norman & Shallice, 1986) is activated.

4.5 The SAS: a consolidated model for understanding many ADHD characteristics

From an information-processing perspective, Norman and Shallice (1986) have used the distinction between automatic and controlled processing to parallel the cognitive processing

required in routine, overlearned situations and in novel, problem-solving situations. The SAS is a theoretical model of the cognitive processes purported to underlie goal-directed behavior necessary in the non-routine situation. It represents a set of cognitive processes involving goal initiation, strategy generation in pursuit of the goal, and evaluation of ongoing performance required to perform complex, non-routine cognitive tasks. The SAS is activated when thought and action schemas representing subroutines capable of realizing a goal effectively cannot be selected through the automatic triggering by well learned cues. The SAS plays a vital role in novel, problem solving situations, where previously well-learned action or thought sequences are inadequate or inappropriate, or where new behaviors need to be planned and monitored for satisfactory performance of the task.

The Supervisory Attentional System (Norman & Shallice, 1986) provides a framework for the conceptualization of executive processing that may be implicated in ADHD. Norman and Shallice's (1986) model of attentional control assumes that two complementary processes operate in the selection and control of action. The basic mechanism is termed *contention scheduling,* which is thought to be able to control routine activities automatically, without conscious control or attentional resources (Norman & Shallice). In non-routine situations requiring novel or difficult actions, the contention scheduling mechanism is modulated by the deliberate, conscious control of the SAS (Norman & Shallice; Shallice, Burgess, Schon, & Baxter, 1989). The components of Norman and Shallice's model are illustrated in Figure 4.1. The model is based on the operation of a series of self-contained, well-learned action and thought sequences termed *schemata* (Norman & Shallice, 1986). A schema can be activated by well-learned triggers, either from the perceptual system or the output of recently active schemata, and is selected once the activation level reaches threshold (Shallice & Burgess, 1991b). The contention scheduling mechanism prevents schemata from conflicting and competing for the same cognitive resource by means of a lateral inhibitory mechanism (Shallice & Burgess, 1991b). However, conflicts between potential action schemata are inevitable and, therefore, a conflict resolution procedure is necessary. The SAS performs this

procedure by modulating the activation level of the schemata, thus biasing their probability of being selected (Shallice & Burgess, 1991b). The higher order processes of the SAS are implicated when the conscious control of action is required.

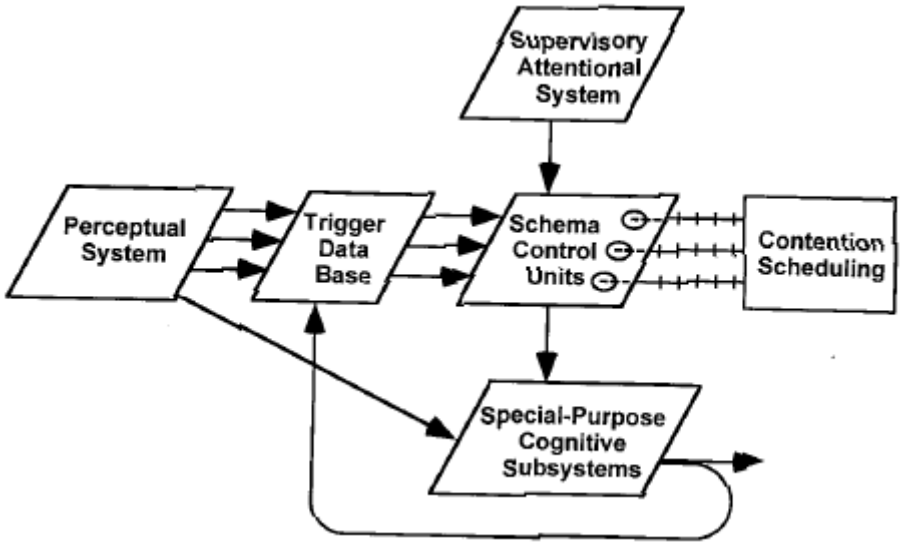


Figure 4.1 The Norman–Shallice model of action control. The arrowed lines represent activating input and the hatched lines represent the inhibitory function of contention scheduling.

An impairment of the SAS should then lead to difficulties in these situations and on tasks that appear to make strong demands on the functions of the supervisory system. Another approach to testing for SAS deficits is to examine tasks that assess the operation of the contention scheduling mechanism unaided by the SAS (Shallice & Burgess, 1993). This is termed *unmodulated contention scheduling.* Shallice (1982) argued that the behavior associated with unmodulated contention scheduling would be dependent on the prevailing task situation. More specifically, a strongly triggered schema will be strongly activated and, in the absence of SAS modulation, will produce "stuck-in-set" perseverative responses controlled by the dominant environmental trigger (Shallice, 1982). Alternatively, in the absence of any strong trigger-schema contingencies, irrelevant aspects of the stimulus situation are likely to capture control of action or thought, resulting in distractibility and impulsive behavior (Shallice, 1982; Shallice & Burgess, 1991b). Shallice (1982, 1988)

documented a number of frontal lobe patients who demonstrated deficits in cognitive processing consistent with those postulated to result from impairment to the SAS. These patients displayed impaired performance in everyday life and on various neuropsychological tests measuring planning, initiation of action, organization, cognitive flexibility, impulsivity, and problem solving (Shallice, 1982, 1988). They typically displayed response perseveration on rule learning tasks and distractibility on continuous performance tasks (Shallice, 1988). In general, these findings provide support for the predictions made from the SAS theory.

In order to refine the tasks which can provide theoretical understanding of the ADHD, two tests have been developed that may have greater promise of tapping the cognitive processes in this area. One is the Six Elements Task (SET) (Burgess et al., 1996), which is a simplified version of the original Shallice and Burgess (1991) test, based on the theoretical model of SAS. Shallice and Burgess (1991) demonstrated that the SET was sensitive to everyday problems associated with goal-directed behavior. Their empirical work showed that patients who were unable to act effectively in everyday life because they experienced impaired attentional control, self-regulation of behavior, and utilization of feedback in carrying out everyday tasks, but who could perform satisfactorily on traditional tests considered sensitive to frontal damage, performed poorly on the SET. The SET has been found to reliably distinguish patients with frontal lobe injury from normal controls, and significant correlations exist between frontal lobe patients' SET scores and observers' objective ratings of their everyday executive problems ($r = 40$; $p < 001$) (Burgess et al., 1998). Because novelty is a critical feature of EF tests, test-retest reliability is often not high on these tests. The SET appears a typical example as Burgess and his colleagues (1996) found moderate test-retest correlations for the SET, which, nevertheless, were similar to those of other EF measures administered at the same time. Unlike most tests of EFs, which are highly structured and in which the goals are provided by the examiner, the SET transfers the tasks of structuring performance and decision-making to the respondent. It measures the individual's ability to schedule his or her performance of a number of simple tasks where the demands are open-ended and where there are a

number of simple rules, which apply across all subtasks. In addition, Shallice and Burgess (1991) claim that, in using this task, the participant's ability to plan, organize, and self-monitor can be studied in isolation from subordinate processes.

The other test in this assessment is the Hayling Sentence Completion Test (HSCT) (Burgess & Shallice, 1996, 1997). The HSCT generates a measure of the ability to generate a strategy in order to fulfil task requirements. Among 91 patients with frontal lesions, poor performances on the HSCT were found among patients with anterior lesions than among age- and IQ-matched patients with lesions to other parts of the brain (Burgess & Shallice, 1996). The HSCT also demands planning and strategy generation. Burgess and Shallice (1996) argue that it is the failure to generate appropriate strategies which underlies poor performance on the HSCT and which leads to the production of errors.

Research examining the functioning of the SAS in ADHD children is limited. However, evidence from the neuropsychological studies discussed previously suggests that the hypothesis of an impaired SAS as the primary deficit in ADHD children is plausible. Further evidence is provided by de Jong and Das-Smaal (1990), who designed the Star Counting Test (SCT) as an attention test for children based on the SAS framework. In a subsequent study, de Jong (1995) demonstrated that the SCT was able to differentiate children identified with attention problems from those without. This provides preliminary evidence in support of the assertion that an impairment of the SAS may be implicated in ADHD. Bayliss & Roodenrys (2000) provided partial evidence of a selective impairment of the inhibitory functions of the SAS, which lends support to fractionation within the SAS (Shallice & Burgess, 1991b). In order to test the SAS they proposed four tasks: the Hayling Sentence Completion Task (Burgess & Shallice, 1996a), the Star Counting Task (de Jong & Small, 1995), the Brixton Spatial Anticipation Test (Burgess & Shallice, 1996b) and the Random Generation Task. Only the Brixton task did not differentiate the children with ADHD from the Normal controls and from the children with LD. The authors concluded that ADHD children do not display the expected impulsivity in responding when there is no strongly activated schema, but do

exhibit difficulty inhibiting strongly triggered responses. This is in accordance with numerous studies that have demonstrated an impairment of inhibitory control in ADHD children (Barkley et al., 1992; Boucugnani & Jones, 1989; Grodzinsky & Diamond, 1992; Schachar & Logan, 1990). Furthermore, these findings are in line with other suggestions that the cognitive model linking executive function deficits to the behavioral symptoms of ADHD is one of inhibition (Pennington & Ozonoff, 1996). In terms of the Norman and Shallice (1986) model, a failure of the SAS to inhibit responses in the presence of dominant environmental triggers may account for the majority of behaviors typically associated with ADHD. The difficulty ADHD children exhibit completing schoolwork, concentrating, and remaining focused can be explained if we accept that once a schema is activated and acted on, the activation level of the schema then begins to decrease. In the absence of the SAS, behavior is open to capture by any number of irrelevant triggers in the environment that are able to activate a competing schema. This will produce a pattern of behavior in which the child seems unable to persist with any activity for more than a short period. Their attention to a task will wane and shift to other, more salient activities or stimuli in the environment, resulting in the impulsive behavior characteristic of these children. In accordance with the subdivisions of the SAS proposed by Shallice and Burgess (1991a), the results of the inhibitory tasks provide support for a specific impairment of the marker creation and triggering component of the SAS in ADHD children. This process is responsible for the interruption of routine ongoing behavior and the initiation of appropriate non-routine action, which appears to underlie the difficulties the ADHD children experienced with these tasks. It could be argued that the Brixton Spatial Anticipation Test, being a rule-learning task, is reliant on the final evaluation component of the SAS in that each move needs to be evaluated for its correctness and the next move re-evaluated or continued.

Chapter 5

Genetics of ADHD

Among the growing literature on ADHD, genetic researches are one of the most promising fields. Genetic analysis may be ordered as a series of related steps in which the questions are increasingly specific conceptual questions concern familiality (*does the disorder run in families?*), heritability (*does the disorder have a genetic component?*), mode of transmission (*is the heritability reflective of a single dominant, recessive, or additive gene, or a number of genes?*), and gene locations. Through the 20th century, most of the work on the genetic basis of ADHD addressed familiality and heritability, but in the last years additional evidence for a defect in a neurotransmitter system has prompted investigations into the molecular genetic basis of the disorder and other evidence point to specific candidates genes in the dopaminergic system (Faraone, 2001; Swanson et al., 2000).

5.1 Family Studies: ADHD aggregates in families

The basic premise of the familial aggregation method is that if there is a genetic component to a given disorder, it should be more prevalent among biological relatives of the proband compared with relatives of controls. Numerous family-genetic studies conducted over the past 30 years have documented a higher prevalence of psychopathology, particularly ADHD, in the parents and other relatives of children with ADHD (reviewed by Faraone & Biederman, 1994). Several early studies reported that ADHD was diagnosed more than five times more frequently among the relatives of ADHD probands than among other families (Biederman et al., 1986). However, first-degrees relatives were also found to have higher rates of other disorders, including conduct disorder, oppositional disorder, anxiety disorder, and affective disorders. This high rate of comorbidity makes it difficult to interpret the findings, because many of comorbid disorders themselves have demonstrated familiality and a genetic etiology. By contrast, the methodological refinements in

further studies permit clarification of the earlier findings. Refinements include the study of psychiatric control groups to evaluate the specificity of findings; assessment of samples referred to pediatric as well as psychiatric clinics to evaluate the impact of sampling procedures; and assessment of comorbidity in probands, to determine whether greater than expected comorbidity could in part results from shared genetic etiology[1] (Perrin & Last, 1996).

Cosegregation analysis of family data provides test of competing hypothesis for the etiology of comorbidity observed between ADHD and other disorders. Basically, ADHD probands are stratified on the basis of the presence / absence of a given co-occurring disorders (e.g. Anxiety, Conduct Disorder, Depression, Learning Disorder). Based on the findings from a series of studies using this approach, Biederman and his colleagues suggest that ADHD and major depressive disorder may show common familial vulnerabilities, ADHD with comorbid conduct disorder may be a distinct subtype, and that ADHD and anxiety disorders as well as ADHD and learning disorders are primarily genetically independent (Faraone et al., 1996).

5.2 Twin and adoption studies: ADHD is heritable

Twin studies of ADHD have been of two major types: 1) comparison of monozygotic (MZ) and dyzigotic (DZ) concordance rates; and 2) multiple regression analysis of data from selected twin pairs. Both methods assume that the shared environment of MZ twins is not greater than that of DZ twins. This assumption may be overly simplistic and may lead to erroneous conclusions about the relative importance of genetic and environmental influences (Plomin et al., 1994). The concordance method provides a test of genetic etiology for dichotomous variables (e.g. presence or absence of ADHD) by comparing the intraclass correlations for MZ and DZ twins. The concordance of genetically based disorders should be higher in MZ twins (who have 100% of their genes in

[1] S*hared environmental factors* are those environmental influences shared by children growing up in the same family; and N*onshared environmental factors* are those environmental influences that make members of the same family different from one another

common) than in DZ-twins (who share only 50% of their genes)[2]. Multiple regression analysis is appropriate when MZ and DZ probands have been ascertained because of deviant scores on a continuous measure and therefore may be used for heritability estimates of ADHD (and component symptoms) conceptualized as a behavioral dimension rather than a categorical disease state. The differential regression of the MZ and DZ co-twin towards the mean of the unselected population provides a test of genetic etiology. Because members of MZ pairs are genetically identical, whereas members of DZ pairs share about 50% of their segregating genes on average, the scores of DZ co-twins should show greater regression toward the mean than those of MZ co-twins if ADHD (or components of ADHD) is due at least in part to genetic factors. The multiple regression method is highly flexible because it provides a statistically powerful test of genetic etiology, a test for differential etiology as a function of both continuous and dichotomous variables, and bivariate applications permit an assessment of the etiology of comorbid conditions, such as ADHD plus learning disability or conduct disorder (DeFries & Fulker, 1985; Silberg et al., 1996; Stevenson, Pennington, Gilger, DeFries, & Gillis, 1993).

On average, studies that used the comparison of correlations between MZ and DZ yield concordance rates for ADHD or components of ADHD (e.g. behavioral symptoms of inattention or hyperactivity, cognitive symptoms of inattention) of .66 for MZ twins and .28 for DZ twins with heritability estimated at .80 (range .50 to .98). Twin studies using regression models also report high heritability estimates for ADHD and components of ADHD, ranging from .75 to .98 (Edelbrock, Rende, Plomin, & Thompson, 1995; Gillis, Gilger, Pennington, & DeFries, 1992; Levy, Hay, McStephen, & Wood, 1997; Sherman, Iacono, & McGue, 1997; Silberg et al., 1996; Stevenson, 1992; Thapar & McGufin, 1995). Moreover, other data suggest that the specific genetic influences are similar (albeit not identical) for males and females (Gjone, Stevenson, & Sundet, 1996) and that the genetic and environmental contributions to ADHD or components of ADHD do

[2] An estimate of heritability (h^2) is obtained by doubling the difference between the MZ and DZ correlations, and an estimation of shared environmental effects (c^2) is obtained by subtracting the heritability estimated from the MZ correlation.

not change from early childhood to adolescence (Gjone et al., 1996). Furthermore, the heritability estimates remain robust across definitions of ADHD or attention problems as part of a continuum of severity or as a categorical disorder, suggesting that ADHD may best be viewed as the extreme end of a behavior continuum that varies genetically throughout the population rather than as a discrete disorder (Gjone et al., 1996; Levy et al., 1997). Also, preliminary evidence suggests that both of the DSM-IV dimensions of inattention and hyperactivity - impulsiveness are heritable and may share a common genetic component (Sherman, Iacono, et al., 1997). The high heritability estimates for ADHD not only imply a very strong genetic contribution, but also a very low level of measurement error. However, it is important to note that the estimated extent of genetic influence varies by informant source and diagnostic criteria. Specifically, heritability estimates are considerably higher for mothers' reports than for teacher reports (e.g. Goodman & Stevenson, 1989; Sherman, Iacono, et al., 1997; Sherman, McGue, & Iacono, 1997) and are higher for ratings of hyperactivity than for psychological measures of attention (e.g. Goodman & Stevenson, 1989).

5.3 The problem of comorbidity

Twin studies have also provided an opportunity to investigate the influence of genetic and environmental factors in comorbidity. The first study to do so was based upon a cross-tabulation of discrete (categorical) measures of ADHD and reading disability (RD), that is by identifying pairs of MZ and DZ twins where at least one member is RD and determining the rate of ADHD in the co-twins (Gilger, Pennington, & De Fries, 1992). A common genetic etiology for ADHD and RD would be indicated by higher cross-concordance for the MZ pairs than for the DZ pairs. The results were consistent with the expected direction (.44 vs. .30, respectively), although the difference was not significant. Gilger et al. (1992) suggested that ADHD and RD are genetically independent, but acknowledged that a genetically mediated comorbid subtype may exist. The genetic and environmental influences on the overlap of ADHD symptoms with oppositional defiant disorder (ODD) and/or CD symptoms have been investigated in two studies (Levy et al., 1997; Silberg et al.,

1996). Findings from the Australian study of a large sample of twins aged 4.12 years old indicate that all of the overlap of ADHD symptoms with ODD and CD symptoms are due to common genetic variance, with genetic correlations of .87 and .95 respectively. By contrast, the overlap between ODD and CD appears to be due to common variance from genetic (63%), shared environmental (28%), and nonshared environmental / measurement error (9%) influences (Waldman, Levy, & Hay, 1995). However, Silberg and colleagues (1996) postulated that the genetic and environmental structure of ADHD and conduct problems might differ at different ages, given the developmental changes in the pattern of association between ADHD and conduct problems from childhood to adolescence (e.g. Weiss & Hechtman, 1993). The inclusion of both younger (8 –11 year-olds) and older (12 - 16-year-olds) twin groups in the Virginia study provided an opportunity to examine the impact of age on comorbidity (Silberg et al., 1996). Consistent with expectations, these investigators found that in the younger cohort, the covariation between hyperactivity and conduct problems was accounted for almost entirely by a common set of genetic influences, whereas in the older group some of the genetic effects are specific to hyperactivity and conduct disturbance, as well as gender-specific (Silberg et al., 1996).

5.4 Identification of Candidate Genes

The identification of candidate genes that may be involved in the etiology of ADHD is advantageous because it is an efficient and statistically powerful approach, and one in which the tight linkage may compensate for problems in accurate diagnosis (Hyman & Nestler, 1993). Genes within the dopamine system are obvious choices for several reasons, including: (1) the effective reduction of symptoms brought about by pharmacological agents that act primarily on the dopaminergic and noradrenergic systems; and (2) results from imaging studies of ADHD that implicate brain structures with rich dopamine innervation, such as the fronto-striatal circuitry (e.g. Castellanos, Giedd, Marsh, et al., 1996). The D4 and DAT1 genes are under careful examination by many research groups interested on ADHD because a major site of action of stimulant drugs is the

dopamine synapse (Civelli et al., 1991). Amphetamine and methylphenidate stimulate the release and/or block the re-uptake of dopamine (Wolkow et al., 1995; Seeman & Van Tol, 1994), which increase the levels of extracellular dopamine in the synaptic space, although presynaptic regulation may change this over time (Solanto, 1998). At clinical doses, this results in decreased activity, inattention, and impulsivity (i.e., decreased symptoms of ADHD). These pharmacological properties of the stimulants were influential in the development of site-of-action theories of ADHD, which focus on possible abnormalities in dopamine pathways of the brain and suggest that the stimulants may correct or compensate for the core deficits of the disorder (Swanson et al., 1998).

The D4 dopamine receptor gene (DRD4), which encodes one of five known protein receptors that mediate the postsynaptic action of dopamine (Civelli, Bunzow, Grandy, Zhou, & Van Tol, 1991), is one potential candidate gene in ADHD. There is evidence that the action of D4 is mostly located neuroanatomically in the dorso-lateral prefrontal cortex (Meador-Woodruff et al., 1994), thereby supporting its purported role in the control of attention. The D4 gene is located on chromosome 11p15.5 and it displays polymorphic variation in human populations (due primarily to a 48-base pair region in the third cytoplasmic loop that can be repeated 2 to 11 times), that may have important implications in susceptibility to neuropsychiatric disorders and response to drug treatment (Lichter et al., 1993; Van Tol et al., 1992). Two independent studies have reported an association of the variable 48-base pair repeat (7-repeat allele) in DRD4 and the personality trait of Novelty Seeking (Shinka et al., 2002). Notwithstanding the need to re-evaluate DRD4 as a candidate gene for personality variation, the similarity of the characteristics of this personality trait (e.g. high levels of impulsive, exploratory, thrill-seeking, and excitable behavior) with those of ADHD have motivated investigations of DRD4 in ADHD. Preliminary evidence exists for an association of the variable 48-base pair repeat in DRD4 and ADHD, with the 7-repeat allele occurring more frequently in the ADHD group (N = 39) than in controls (N = 39), matched for age, ethnicity, and gender (LaHoste et al., 1996). Although that study used a case control design that is prone to bias due to population stratification, the findings have been replicated in other separate

clinical samples with appropriate controls, using the robust HRR method (Sunohara et al., 1997). The results for the increased frequency of the 7-repeat allele in the ADHD groups are interesting because expression of the 7-repeat allele in vitro mediates a blunted cellular response to dopamine (Ashgari et al., 1995).

Faraone and colleagues (2001) analysed nine papers which used the "case control" method (*Do children with ADHD have a different pattern of alleles in the DRD4, i.e. higher presence of the 7 repeat allele*?). Five of them were statistically significant and overall the effect of the gene on the diagnosis was modest bus significant (Odd Ratio = 1.9). Farone and colleagues (2001) analysed also 14 studies that used the "the family transmission" method (*Do parents trasmitt more frequently the risk allele that cause the pathology?*) and they found out that the effect of the 7 repeat allele is even lower (Odd Ratio = 1.4) but it remains statistically significant. These results confirmed a small, but significant causal role of the DRD4 gene in the ADHD etiology. According to Mill et al., (2001) this result could be due to the stratification of the population.

An Israeli group (Manor et al., 2002) tested 131 ADHD patients administering the TOVA battery (Test Of Variables of Attention, Greenberg & Waldman, 1993), splitting the patients on the basis of the presence or not of the 7 repeat allele in the D4 gene. They, surprisingly, found out that those children with the 2-5 repeat allele made more commission errors and had slower correct responses compared to those children with the 6-9 repeat allele. This study replicated the study by Swanson et al. (2000) in which ADHD children with the 2-4 repeat allele (no-risk allele) have more neuropsychological impairments than those with the risk allele. These controversial results could also be understood controlling for comordity; and in this direction Holmes et al. (2002) analysed the role of the DRD4 gene and the comorbidity in patients with ADHD, and they concluded that there is stronger association between the DRD4 gene and the diagnosis of ADHD + Conduct Disorder than ADHD alone.

In summary, it is still debated how much of the variance, of the ADHD etiology, could be accounted by the presence of the 7 repeat allele of the DRD4 gene, in fact according to Ding et al.

(2002) the 7 repeat allele is different from the 2-6 repeat because it shows more recombinations/mutations suggesting that this allele is 5-10 fold younger than the common 4 repeat allele. Ding et al. (2002) proposed that this allele originated as a rare mutational event that nevertheless increased to high frequency in human population by positive selection.

Another candidate gene involved in the ADHD etiology is the dopamine transporter gene (DAT) because many pharmacological agents used in the treatment of ADHD inhibit the dopamine transporter (e.g. methylphenidate, dextroamphetamine, pemoline, buproprion). Moreover, there is preliminary evidence of an association between one allele (480-bp) of the dopamine transporter locus (DAT1) and ADHD (Cook et al., 1995). This association (preferential transmission of the 10 repeat allele) has been replicated in a second study by Gill et al. (1997), using the same haplotype relative risk (HRR) method. It is not known whether the DAT1 VNTR[3] allele has functional significance itself, is the result of linkage disequilibrium, or simply a false positive (Gill et al., 1997). In a third study, Daly et al. (1999) reconfirmed their previous finding (Gill et al 1997) of preferential transmission of the 480-bp allele using a new sample (one-tailed p = .039) and a previously reported sample (odd ratio relative risk = 1.2, p = .006). The relationship between DAT1 and ADHD was also examined by Waldman et al (1998), who reported evidence for linkage of ADHD with DAT1, obtained using the transmission disequilibrium test (TDT). This relationship was especially strong for the combined subtype but not the inattentive subtype. In an additional analysis, the symptoms of the probands were regressed on the number of 480-bp repeat alleles for each proband (n = 112). The number of 480-bp repeat alleles was reported to be significantly related to the number of hyperactive-impulsive symptoms but not to inattentive symptoms.

The *DAT1* findings are of particular interest since stimulant drugs interact directly with the transporter protein. Winsberg and Comings (1999) examined the correlation between response to methylphenidate treatment and *DAT1* genotype in a series of 30 African-American children with

[3] VNTR (variable number of tandem repeat) are regions of DNA that are composed of repetitive DNA sequence (tandem repeat) of no known function. VNTR is one of the major types of DNA polimorphisms used as linkage markers.

ADHD. Of the responders, only 31% carried the 10/10 genotype while 86% of the non-responders carried the 10/10 genotype (p = 0.008), suggesting that in this population 10/10 homozygosity is associated with a poor response to stimulant treatment. To date, there have been nine published association studies of ADHD with a 480 bp allele of a variable number tandem repeat (VNTR) polymorphism in the 3'-untranslated region of the gene: five support an association and four do not (summarised by Curran et al, 2001b). Meta-analysis of these data is consistent with a very small main effect for the 480 bp allele and is not yet convincing ($[X]^2$=3.45, P=0.06, OR=1.15). However, there is significant evidence of heterogeneity between the combined data-sets (X^2=22.64, d.f.=8, P=0.004), suggesting that the studies may divide into two groups: those in which the associated *DAT1* allele has a main effect and those in which the allele does not. In this case, failure to replicate the association in some studies may result from variation in the strength of the genetic influence in different populations. The cause of such heterogeneity remains unknown and requires further investigation. The interactive effects of comorbidity and DAT1 gene had been analysed by Young et al., (2002) and they found a stronger role of the 9-repeat allele is a significant risk allele for externalizing behaviors in children with ADHD at ages 4, but not at 9.

To date only two studies analyzed the combined effects of the DRD4 and the DAT1 genes (Rowe et al., 2001; Roman et al., 2001). Rowe et al., (2001) demonstrated (with a clinical group of 80 fathers and 107 mothers, and a control group of 42 fathers and 51 mothers) that there is a stronger association of the 7 repeat allele of the DRD4 and hyperactivity-impulsivity in fathers and the 10/10 repeat allele of the DAT1 and inattention in mothers. Roman et al. (2001) analyzed the association with both the DRD4 gene and the DAT1 and ADHD: they observed an excess of the DRD4 7 repeat allele in the ADHD group (probands and parents), but they did not observed the effect for the 10/10 repeat allele. However, HRR analysis showed no preferential transmission of both DRD4 and DAT1 risk alleles; nevertheless an interaction effect of both genes on ADHD hyperactive-impulsive dimension was observed ($F = 4.68$; $p < .03$). Other researches are necessary to analyse the combined effect of more than one gene. In this direction, only one paper is published presenting

results using a genowide scan (Fisher et al., 2002): the authors analysed 126 affected sib pairs and they indicated that it is unlikely to find out a major gene involved in ADHD etiology. Qualitative trait maximum LOD scores higher than 1.5 were found on 5p12, 10q26, 12q23 and 16p13 chromosomes. None of these regions includes DAT1 or DRD4 genes, but only three of the candidate genes (DRD5, 5HTT and CALCYON) coincided with sites of positive linkage found by this screen. Two of the regions highlighted by Fisher et al. (2002), 2q24 and 16p13, coincide with the top linkage peaks reported by a genome-scan study of autistic children.

In conclusion, candidate gene studies show an inconsistent pattern of replication (Faraone et al 2005), and the three research groups that have conducted genome scans of ADHD thus far have identified largely nonoverlapping chromosomal regions as potentially harboring susceptibility genes (Arcos-Burgos et al 2004; Bakker et al 2003; Fisher et al 2002; Ogdie et al 2002). Such inconsistencies, although often found in complex phenotypes in which multiple genetic and nongenetic factors are acting in concert, present challenges to understanding the genetic architecture of ADHD.

Chapter 6
Participants

6.1 Study 1

Children with ADHD were diagnosed using the Italian version of the DICA-R (Diagnostic Interview for Children and Adolescent-Revised) (DICA-R, Reich et al 1995; Battaglia et al. 1997) following DSM-IV criteria (APA, 1994). The presence of Conduct Disorder (CD), Mood Disorder or Anxiety Disorder were exclusion criteria. In order to confirm this diagnosis, the Disruptive Behavior Disorder (DBD) Rating Scales for Parents and Teachers (Marzocchi et al., 2001; Marzocchi et al., 2003) were completed. The cut-off criteria of the Disruptive Behavior Disorder (DBD) Rating Scales for Parents and Teachers was the 90^{th} percentile according to both parents and teachers. Normative data for the DBD Rating Scale are based on a sample of 1085 Italian children rated by both parents and teachers (Marzocchi et al., 2001; Marzocchi et al., 2003). All patients undergo a comprehensive neurological and medical examination. No child had a history of brain damage, epilepsy, psychosis or language disorder.

The sample included 31 children with Attention Deficit Hyperactivity Disorder (ADHD) (29 males, 2 females) and 33 normal controls (NC) (28 males, 5 females) aged 7-12. Two sub-groups, divided by age, were considered: 7-8 years (ADHD = 10; NC = 16) and 9-12 years (ADHD = 21; NC = 17). All patients were recruited from ”Child Psychiatry Units” of “IRCCS E. Medea” in Northern Italy: 19 from Conegliano and 12 from San Vito al Tagliamento. Normal control children were recruited from primary schools in the same area as two clinics of the “IRCCS E. Medea” (Conegliano and San Vito al Tagliamento).

The cognitive development was assessed administering four subtests of the WISC-R (Vocabulary, Arithmetic, Block Design and Picture Arrangement): these subtests were chosen because they correlate .93 to .95 with the full administration of the WISC-R (Groth-Marnat, 1990). Children who had an IQ score below 80 were excluded. The two groups were matched for gender (χ^2

(1) = 1.24, n.s.), for Performance IQ (t (62) = 0.69, n.s.), and for age (t (62) = 1.45, n.s.), but not for Verbal IQ (t (62) = 3.55; $p < .001$) and for Full Scale IQ (t (62) = 2.73; $p < .01$) The presence of significant differences between groups concerning VIQ and FSIQ is due to the significant difference in performance between groups on the Arithmetic subtest of the WISC-R (t (62) = 3.89; $p < .001$). The Arithmetic subtest was included in this short version because the literature (Groth-Marnat, 1990) suggested that by combining these four sub-tests one can obtain the highest correlation values with FSIQ. Actually, the inclusion of the Arithmetic subtest may cause problems in the matching of children with ADHD and / or Dyslexics, because the planning deficits of children with ADHD may also impair the arithmetical performance and because about 40% of children with Dyslexia also present with Developmental Dyscalculia (Shalev, Auerbach, Manor & Gross Tsur, 2000).

In child neuropsychology, the procedure for matching between normal controls to disordered children is always problematic, because the tests for assessing "general intelligence" are not able to extract a pure measure of this construct. Normally, adeguate performance of the sub-tests of the WISC-R require appropriate linguistic, arithmetical, perceptual, planning or visuo-spatial skills that are, in many cases, not functioniong perfectly in children with Learning Disabilities or ADHD. For these reasons, in the literature it is frequently debated whether the control group must be perfectly matched to the neuropsychologically impaired groups. A perfect match, probably selects neuropsychologically disordered children with higher level of "general intelligence" compared to controls, so the interpretations of the performance on other experimental tests may be problematic because the groups are not truly matched. On the other hand, it has even been suggested that one should avoid a perfect match between controls and disordered children, in order to obtain average groups of children (with or without a disorder) and not bias the subject selection procedure.

Age and symptoms severity results are summarized on table 6.1. Means and standard deviations for the subtests of the WISC-R and IQ are summarized in table 6.2.

Table 6.1.

Subject characteristics: age and symptoms of ADHD and Oppositional Defiant Disorder (ODD)

(study 1)

Measures	ADHD 7-8 yrs. (n = 10) Mean (SD)	ADHD 9-12 yrs. (n = 21) Mean (SD)	Controls 7-8 yrs. (n = 16) Mean (SD)	Controls 9-12 yrs. (n = 17) Mean (SD)
Age	7.70 (0.48)	10.10 (1.09)	7.56 (0.51)	10.09 (1.09)
Inattention P.	15.80 (5.59)	14.86 (5.53)	3.50 (2.25)	5.94 (3.98)
Hyperactivity P.	17.00 (2.54)	12.38 (6.14)	2.69 (2.18)	4.41 (3.71)
ODD P.	7.50 (1.84)	4.67 (2.61)	2.33 (2.31)	0.33 (0.58)
Inattention T.	15.78 (7.92)	17.48 (4.75)	2.00 (2.25)	4.27 (3.33)
Hyperactivity T.	12.33 (7.02)	13.05 (7.21)	1.36 (2.68)	2.00 (2.80)
ODD T.	4.67 (2.18)	4.19 (2.77)	1.88 (1.90)	1.12 (1.91)

Note: Inattention, Hyperactivity and ODD are values obtained from the DBD Rating Scales (the range is between 0 to 27). P. = Parents; T. = Teachers. Max values are 27 for Inattention and Hyperactivity, and 24 for ODD.

Table 6.2.

WISC-R results (study 1).

Measures	ADHD 7-8 yrs. (n = 10) Mean (SD)	ADHD 9-12 yrs. (n = 21) Mean (SD)	Controls 7-8 yrs. (n = 16) Mean (SD)	Controls 9-12 yrs. (n = 17) Mean (SD)
Full Scale IQ	97.20 (11.32)	100.29 (9.15)	104.06 (5.80)	105.88 (7.03)
Verbal IQ	94.10 (10.20)	92.57 (7.70)	97.94 (12.30)	104.35 (5.61)
Performance IQ	100.80 (13.22)	108.57 (15.90)	110.81 (9.85)	106.12 (13.64)
Vocabulary	8.86 (2.48)	9.05 (2.34)	9.31 (2.43)	10.82 (1.78)
Arithmetic	8.43 (2.51)	8.21 (2.25)	10.69 (3.04)	10.82 (2.01)
Picture Arrangement	10.00 (2.45)	10.89 (3.09)	10.88 (1.60)	10.41 (1.78)
Block Design	10.00 (3.00)	11.53 (2.78)	12.19 (1.69)	11.41 (2.68)

6.2 Study 2

In the study 2 the same assessment procedure of the study 1 was followed (DICA-R interview with parents, DBD Rating Scale for Parents and Teachers), but a third centre of the "IRCCS E. Medea" (Bosisio Parini in Lombardy) was involved in the research. In the study 2 the Digit Span measure was obtained with the administration of the WISC-R. Moreover, in the study 2 the reading performance was assessed in order to separate the ADHD children with or without Reading Disorder (RD) and to recruit a second control sample of children with RD. Therefore in the study 2 four groups of children were considered: ADHD-only, RD-only, ADHD+RD and Normal Controls. The reading performance was assessed by two Italian standardized tests, namely the MT Test of text reading (Cornoldi, Colpo & Gruppo MT, 1998), and the three lists of Pseudo-words (Sartori, Job & Tressoldi, 1995). Inclusion criteria for a diagnosis of RD were performing at least 1.5 Standard Deviations below the mean on the MT Test (on both Speed and Accuracy) and at least 2 Standard Deviations below the mean on the three lists of Pseudo-words (and both Speed and Accuracy).

One hundred thirty-one children were selected: 37 Normal Controls (31 males and 6 females), 38 with ADHD-only (34 males and 4 females), 39 with RD-only (30 males and 9 females), and 17 with ADHD + RD (16 males and 1 females). Geographically, the patients were divided in the following way: of the 38 ADHD-only patients, 16 were from Veneto, 4 from Friuli and 18 from Lombardy; of the 39 RD-only patients, 9 were from Veneto and 30 from Lombardy; of the 17 ADHD+RD patients, 3 were from Veneto, 6 from Friuli and 8 from Lombardy. Control children were recruited from primary schools (from 2nd to 7th grade) in Veneto and Friuli. Their scores on DBD Rating Scale were between the 60th to the 30th percentile. Informed consent was obtained from all children and their parents. The Object Rapid Naming is a sub-test of a battery on pre-requisite of learning (Cornoldi & Gruppo MT, 1993).

6.2.1 Children with ADHD and Controls for replicating study 1

In order to replicate the study 1 we have considered only two groups: Normal Controls (N = 37) and with ADHD (N = 55) ignoring the RD status. Children of the two groups were not matched for age, and for this reason in the successive analysis age was covariate. Age and the severity of ADHD and ODD symptoms are reported on table 6.3. Means and standard deviations for the subtests of the WISC-R and IQ are summarized in table 6.4.

Table 6.3.

Subject characteristics: age and symptoms of ADHD and ODD (study 2; RD excluded)

Variables	ADHD 7-8 yrs. (n = 26)		ADHD 9-12 yrs. (n = 29)		Controls 7-8 yrs. (n = 9)		Controls 9-12 yrs. (n = 28)	
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Age	8.07	(0.64)	10.41	(1.08)	8.12	(0.51)	11.11	(1.18)
Inattention P.	15.85	(6.56)	14.07	(4.27)	4.78	(2.73)	3.96	(3.01)
Hyperactivity P.	16.46	(4.22)	13.72	(4.50)	3.89	(2.85)	3.39	(2.53)
ODD P.	8.54	(4.14)	6.00	(3.39)	0.50	(0.70)	3.67	(1.73)
Inattention T.	17.39	(5.94)	18.21	(4.61)	6.00	(6.87)	2.28	(2.67)
Hyperactivity T.	18.52	(6.16)	17.79	(5.34)	3.00	(5.87)	1.58	(2.04)
ODD T.	10.41	(6.77)	9.93	(4.24)	2.50	(0.71)	2.67	(2.74)

Note: Inattention, Hyperactivity and ODD are values obtained from the DBD Rating Scales (the range is between 0 to 27). P. = Parents; T. = Teachers. Max values are 27 for Inattention and Hyperactivity, and 24 for ODD.

Table 6.4.

WISC-R results (study 2; RD excluded)

Measures	ADHD 7-8 yrs. (n = 26) Mean (SD)	ADHD 9-12 yrs. (n = 29) Mean (SD)	Controls 7-8 yrs. (n = 9) Mean (SD)	Controls 9-12 yrs. (n = 28) Mean (SD)
Full Scale IQ	103.96 (11.63)	100.54 (11.78)	102.33 (6.84)	102.68 (7.68)
Verbal IQ	100.92 (10.06)	95.32 (8.88)	105.89 (10.98)	99.39 (9.46)
Performance IQ	106.54 (15.59)	106.71 (15.63)	98.33 (10.72)	105.96 (13.28)
Vocabulary	9.63 (2.06)	9.18 (1.87)	11.33 (2.45)	10.11 (2.10)
Arithmetic	9.67 (2.08)	8.89 (2.06)	10.00 (1.50)	10.04 (1.99)
Picture Arrangement	11.33 (2.78)	10.18 (3.03)	9.78 (1.64)	10.04 (2.57)
Block Design	10.58 (2.72)	11.57 (2.60)	9.78 (1.72)	11.61 (1.87)
Digit Span	8.24 (2.86)	8.45 (2.77)	11.73 (3.07)	10.91 (2.92)

6.2.2 All participants of the study 2

On table 6.5 the age and the severity of the ADHD and ODD symptoms of all participants of the study 2 are reported, and on the table 6.6 the WISC-R data and the reading performance are summarized. The participants differed somewhat with regard to the mean age (ADHD-only and ADHD+RD were significantly younger than RD-only and Normal Controls; $F(3,127) = 8.61$, $p < .05$), for this reason in the following analyses, age was covaried. Not unexpectedly, children with RD-only had somewhat more problems of attention and hyperactivity than Normal Controls: they had been rated significantly more inattentive ($p < .05$) and significantly more hyperactive-impulsive ($p < .05$) than Controls according to their parents; and significantly more inattentive ($p < .05$) than Controls according their teachers. Children with RD-only gave significantly poorer performance on the two verbal sub-tests of the WISC-R (Vocabulary, $p < .05$, and Arithmetic, $p < .05$) than Normal Controls. Therefore the Verbal IQ of the children with RD-only and ADHD+RD was significantly

lower than the Verbal IQ of the Normal Controls ($p < .05$), but the Performance IQ and the Full Scale IQ values were not different between the four groups.

The reading performance is reported on *z* scores: the mean is 0 and the standard deviation is 1, so a score higher than 0 means a good performance and a score lower than 0 means a poor performance. Obviously, the children with RD were severely impaired in reading and in Object rapid naming as shown in table 6.6, in particularly with pseudo-words ($p < .001$).

Fourteen ADHD children of study 2 were already tested in study 1, however only three tasks of the battery may present a learning effect (Letter Fluency, Junior Hayling and Junior Brixton), and the rest of the tasks was different from those presented in study 1 (TEA-Ch, Strategic Memory Task, Semantic Fluency) or they have been modified (SART, Vigilance Task and Number Stroop). Moreover, preliminary analysis on the three tasks which may present a learning effect revealed that the performance of the 14 children already tested in study 2 was not different from the performance of the 41 ADHD children tested only in study 2. For these reasons in study 2 I decided to not differentiate children already tested in study 1.

Table 6.5.

Subject characteristics: age and symptoms of ADHD and ODD (RD included; study 2)

	ADHD-only (n = 38)		RD-only (n = 39)		ADHD+RD (n = 17)		NC (n = 37)	
Variables	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Age	9.21	(1.38)	10.70	(1.30)	9.52	(1.71)	10.26	(1.60)
Inattention P.	14.08	5.49)	10.03	(4.90)	16.76	(5.17)	4.57	(3.35)
Hyperactivity P.	14.87	(4.01)	6.37	(3.24)	15.35	(5.68)	3.62	(2.55)
ODD P.	7.53	(3.72)	3.26	(3.08)	6.47	(4.43)	3.27	(1.90)
Inattention T.	17.83	(5.26)	11.74	(5.32)	17.87	(5.29)	3.97	(4.54)
Hyperactivity T.	18.83	(5.23)	3.71	(3.25)	16.40	(6.49)	1.94	(3.40)
ODD T.	10.39	(5.49)	2.48	(3.25)	9.50	(5.46)	2.55	(2.50)

Note: Inattention, Hyperactivity and ODD are values obtained from the DBD Rating Scales (the range is between 0 to 27). P. = Parents; T. = Teachers. Max values are 27 for Inattention and Hyperactivity, and 24 for ODD.

Table 6.6.

WISC-R results and Reading Performance (RD included; study 2)

	ADHD-only (n = 38)		RD-only (n = 39)		ADHD+RD (n = 17)		NC (n = 37)	
Variables	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Full Scale I.Q.	103.89	10.89	99.08	8.23	98.47	12.84	103.38	8.24
Verbal I.Q.	98.57	9.89	93.77	10.46	96.53	9.64	101.33	10.32
Performance I.Q.	109.26	13.55	105.83	11.06	101.24	18.05	105.15	13.45
Vocabulary	9.34	2.03	8.63	3.12	9.47	1.84	10.33	2.23
Arithmetic	9.54	1.92	8.38	2.19	8.65	2.34	10.21	2.00
Picture Arrang.	11.11	2.94	11.40	2.33	9.88	2.87	10.18	2.47
Block Design	11.43	2.34	11.11	2.49	10.47	3.24	11.23	1.95
Digit Span	8.71	2.95	7.38	2.41	7.50	3.32	11.18	2.95
Text: accuracy	-0.13	0.65	-2.27	1.97	-2.90	3.93	0.14	0.61
Text: speed	0.02	0.52	-3.10	2.66	-3.24	3.52	0.33	0.31
No-words: accur.	-0.55	1.24	-3.02	2.11	-2.23	2.43	0.10	0.94
No-words: speed	-0.80	1.16	-3.39	2.72	-3.88	2.74	0.16	1.04
Rapid Obj. naming	80.0	23.4	87.0	23.1	98.9	26.6	113.16	39.28

Note: Read text: MT Test (Cornoldi, & Gruppo MT, 1998); Read Pseudo-words (Sartori, Job & Tressoldi, 1995); Reading Performance are presented in Z scores (Speed and Accuracy). IQ values are obtained from the WISC-R (Wechsler, 1994) and Obj. Rapid Naming is a sub-test of the "Prove di prerequisito per la diagnosi delle difficoltà di lettura e scrittura; Cornoldi & Gruppo MT, 1992). Contrasts are significant at Alpha = 0.05. * $p < .05$, ** $p < .01$, *** $p < .001$.

An attempt to subdivide the group of children with RD was carried out in order to check whether Coltheart's model (1978) is plausible considering the Italian language. The performance on the lists of words and non-words was considered. Since, the Italian language is a transparent one, a composite score of speed and accuracy was obtained for the two types of lists (words and non-words), then the cut-off of 1 standard deviation below the means of the

national norms was used. If a child performed 1 SD below the mean, or worse, only on the list of non-words he was classified as phonological dyslexic; if a child performed 1 SD below the mean, or worse only on the list of words he was classified as surface dyslexic; if a child performed 1 SD below the mean on both types of list, he was considered a mixed-type dyslexic. Only 1 child was classified as phonological dyslexic, 2 children were classified surface dyslexics and 36 children were classified as mixed dyslexics. Therefore, mostly in the Italian context the pure subtypes of developmental dyslexia are hardly found, and any type of comparisons between sub-groups of dyslexics becomes difficult to apply.

Chapter 7

Executive Function as assessed by analogues of adult tests for prefrontal function in children with ADHD and / or RD: Hayling, Brixton and Fluency tests

7.1 Introduction

The present experiments have a number of different aims: the first concerns the specificity of the organic hypothesis. As discussed in the Introduction, at least three rather different positions exist in the literature in which an analogy is drawn with the effects of adult brain damage. Disorders of inhibition and of attentional systems have major overlaps with disorders of executive functions but they are also much more specific. We will treat them on the whole as being more specific hypotheses within the general overall executive function deficit position; that they result from a damage to a higher-level Supervisory System (Shallice, 1982; Norman & Shallice, 1986) - such a high-level system most likely has a number of separable subsystems (Shallice & Burgess, 1996).

The second aim was to analyze new tests known to be affected by prefrontal lesions and which were capable of being adapted to the testing of children in the 7-12 year old range. Two new tests – the so-called Hayling Sentence Completion Test (Burgess & Shallice, 1996a, 1997) and the Brixton Spatial Rule Attainment Task (Burgess & Shallice, 1996b, 1997) have been studied.

A third aspect of the present experiment is to use executive function tests which are directed towards specific Supervisory functions and which have a number of different measures which load on different underlying executive function components. Using such tests should increase the possibility of obtaining dissociations within executive function measures. In general, therefore we avoided complex multi-component tasks such as the Wisconsin Card-Sorting or Tower tasks.

The first test to be examined was a developmental version of the Brixton Test in which the subject must guess which one of 10 numbered drawing of turtles will be coloured on the following card. Successive cards obey a rule such as increase or decrease by one; stay on 9; or switch between 5 and 10, and between 4 and 9. Thus subjects must abstract the rules. The task was derived

conceptually from the Wisconsin Card-Sorting Task (Milner, 1964) since it requires the subject to switch from one rule to another. However while it, too, is affected by frontal lesions, it differs in two main respects apart from the domain in which the rules lie. The first is that as the rules relate to the relation between successive cards; they are more abstract. Second, the rules are not over-learned; rules switch in an unpredictable manner at the same place for all subjects, every 5-8 cards rather than after the subject has been correct for 6 or 10 trials, as in different versions of Wisconsin Card-Sorting (Heaton, 1981). As a result the characteristic "frontal" error tends not to be one of perseveration, as in Wisconsin Card-Sorting, but making a guessing response which is unrelated to the responses normal subjects make in that type of situation. The Brixton too has a second frontal characteristic, which does not correlate with overall error rate and the tendency to produce guessing responses. This is the tendency to give up obeying an already obtained rule, before the next rule switch occurs. Bayliss and Roodenrys (2000) presented children with ADHD or Learning Disability with the Brixton and the Hayling task (the Hayling will be described below), and they found that ADHD children were not impaired on the Brixton task, but were on the Hayling. The authors (Bayliss & Roodenrys, 2000) concluded that the group of ADHD was impaired in tasks that require the inhibition of a strongly triggered response (Junior Hayling) whereas they were not impulsive in responding when there is no strongly activated schema (Brixton task). The group of Learning Disabled children did not show any difficulty in the Executive Function domain.

The second test is the Hayling Test which requires the subject to complete a sentence frame, namely a sentence missing its final word, in one of two conditions. In the first part of the test – Hayling A – the subject has to complete the sentence with the appropriate word. In Hayling B, the subject must complete the sentence frame with a word that makes no sense and is unrelated to all the words in the frame. This means that the dominant responses must be inhibited; however this process occurs without the strong time pressure of the more familiar Stroop and Stop Tasks. However another factor in the test is that normal subjects tend to develop a strategy to avoid being placed in the difficult situation of having to think of a response which will <u>not</u> fit the sentence frame

when the completion has already come to mind. They therefore produce a response before they hear the sentence frame and check that it does not fit with the frame when the frame is read out to them. The two most usual strategies used to produce the response are to think of a word related to the previous response or to select an object in the room. Frontal patients are impaired on both aspects of the task. Burgess & Shallice (1996a) presented ninety-one patients with cerebral lesion with the Hayling test: only those with frontal lesion were slower in section A (where the sentences must be completed with the right word) and less accurate in the section B (where the sentences must be completed with a semantically unrelated word). Moreover, frontal patients also produced fewer words which indicated the use of a strategy during response preparation.

Clark et al. (2000) presented four groups of adolescents (ADHD, Conduct Disorder – CD, ADHD+CD, and Normal Controls with the Hayling and also the Six Element tests (Burgess et al., 1996). The two groups of adolescents with ADHD (ADHD-only and ADHD+CD) were impaired on both the Hayling and on the Six Element test, but the group with Conduct Disorder was not impaired. Clark et al (2000) concluded that, among the Externalized Disorders (ADHD and CD), Executive Function and strategy application impairments are specific for the subjects with ADHD and they are not generalized also to Conduct Disorder.

To our knowledge, three neuroimaging studies (PET) on the Hayling test have been published so far: Nathaniel-James, Fletcher and Frith (1997); Collete, Van der Linden, Delfiore, Luxen and Salmon (2001); and Nathaniel-James and Frith (2002) and two lesion studies (Burgess and Shallice, 1996a; Andrés and Van der Linden, 2001). Nathaniel-James and Frith (1997) presented six normal adults with a visual version of the Hayling test (the sentences were shown on a computer screen), in which the subjects were asked to complete the sentence with an appropriate word (response initiation) or with a word which made no sense in the context (response suppression). The results of this study showed that response initiation and response inhibition were associated with inferior frontal gyrus and right anterior cingulate gyrus activation. Response activation was specifically associated with left frontal operculum and middle temporal gyrus

activation. Response suppression was specifically associated with left temporal operculum activation.

Collete, Van der Linden, Delfiore, Luxen and Salmon (2001) presented (on a computer screen) twelve young subjects (from 21 to 28 years old) with a set of 270 sentences: one third for a reading condition, one third for response initiation and one third for a response inhibition condition. The comparison of the initiation condition to the reading condition showed an increase of activity in the left inferior frontal operculum (BA45/47) (as obtained by Nathaniel-James & Frith, 1997). When the inhibition condition was compared to the initiation condition, an increased activity was found in a network of left prefrontal areas, including the middle (BA9 and BA10) and the inferior (BA45) frontal areas.

In a second study, Nathaniel-James and Frith (2002) controlled for the level of constraint of the missing word of the section B of the task: low constraint means that the sentences could be completed with several possible words, whereas high constraint means that the sentences could be completed with only one possible word. With all levels of constraint combined, significantly greater activation was observed in the left DLPFC (BA46/9) under the suppression condition and in the medial orbitofrontal cortex (BA11) under the initiation condition. Under the high-constraint condition with both tasks combined, significant right middle temporal activity (BA21) was observed, whereas under low constraint, the left DLPFC was significantly activated. An interaction of task by constraint revealed that the left DLPFC was significantly more active in the suppression task at all levels of constraint, but only under the low-constraint conditions in the initiation task. When the level of constraint was higher the right middle temporal lobe became more active.

The third test to be used is Verbal Fluency, because most previous studies (e.g. McGee et al., 1989; Fischer et al., 1990; Loge et al., 1990) had not found an ADHD effect, although a few (Grodzinsky & Diamond, 1992; Mahone et al, 2001) did find significant effects. We, however, also examined the time course of generation, as the most frequent frontal sign is for a rapid reduction in number of responses as the attempt to generate words continues (Stuss et al., 1998). The Letter

Fluency task is associated with left prefrontal cortex functioning which requires the generation of words that begin with a specified letter (Paulesu et al., 1997; Gaillard et al, 2003). Patients with bilateral medial or left lateral frontal lesions but not right lateral frontal lesions have been found to generate significantly fewer words than matched controls (Janowski et al, 1989; Stuss et al., 1998); thus, poor performance on Letter Fluency, relative to Semantic Fluency, is considered evidence of executive dysfunction (Denckla, 1994). Moreover, frontal lesioned patients also showed a rapid decrease of word production during the task (Stuss et al., 1998), and for this reason in this study we were interested to the production of words across one minute.

Levin, Song, Edwing-Cobbs, Chapman and Mendelsohn (2001) analysed the performance of children with Closed Head Injury (CHI) on a verbal fluency task in order to look for specific deficit according to the site of the lesion and the age of the children. The older children with left frontal lesion were significantly more impaired than the patients with lesions on other areas (temporal, occipital, parietal and corpus callosum). In the younger children group, those with left frontal lesion were not significantly impaired. The authors (Levin et al., 2001) concluded that there is an interaction age by site of lesion because only the oldest children with left frontal lesion were impaired on the verbal fluency task, so it seems that the specialization of the left side for the Verbal Fluency task became evident during pre-adolescence.

7.2 Study 1

7.2.1 Material

a. The Junior Brixton Spatial Rule Attainment Test

The Junior Brixton consisted of 45 cards each having 10 turtles (9 grey and 1 green). The participants were presented with the cards one at time which differed only in the position of the green turtle. The position of the green turtle changed according to 5 rules which changed every 9 trials. The subject must guess which one of 10 numbered drawing of turtles will be coloured on the following card. Successive cards obey a rule such as increase or decrease by one; stay on 9; or switch between 5 and 10, and between 4 and 9.

Three types of errors had been coded: Perseverations or "error type 1"; Plausible responses or "error type 2"; Guessing responses or "error type 3". A Perseveration error was coded if the child gave a response that was congruent with a previous rule: e.g. in the second block of trials where the rule is "- 1" (the turtle is going backward), if the child saw the target in the position number 4 and pointed to the position number 5, this means that he thought that the rules was "+ 1" (the turtle is going onward), that was the previous rule. Furthermore a perseveration of response was coded, when the child incorrectly repeated pointing to the same position of the green turtle. Finally, if the child pointed to the green turtle seen on the card, if it was an error it is again Perseveration, because s/he is "captured" by the stimulus instead of generating a plausible rule.

"Error type 2" or Plausible errors are considered as those incorrect responses in which the child tried to figure out a spatial rule without giving a perseveration response. Plausible rules are those in which a child pointed to a turtle close to the stimulus (top, down, left, right on a diagonal with respect to the green turtle on the card).

"Error type 3" or Guessing responses are all other type of errors in which the child did not try to figure out a plausible spatial rule and s/he did not make a perseveration. All responses in which the pointed turtle is not close to the stimulus (green turtle on the card) are considered Guessing responses.

b. Junior Hayling Sentence Completion Task

The Junior Hayling consisted of 20 sentences in which the final word was missing. The sentences were divided into two sections (A and B) each containing 10 sentences. The missing words were matched for frequency and age of acquisition. In section A, children were asked to complete the sentence with a word that fitted the phrase, so the maximum score is 10. In section B, following the procedure of the adult Hayling test (Burgess & Shallice, 1996a; 1997) children were asked to produce a word which made no sense at all in the context of the sentence. The children were told that the word had to be completely unrelated to words in the sentence. Response times were recorded using a stop-watch. Two practice sentences were read to the participants before each section. The scoring in section B was calculated using the standard Hayling procedure, as follows:

0 = if the child said a word unrelated to the sentence (U-type responses). These responses were subdivided according to whether they fitted into the two strategies most used by adults (see Introduction): UR responses, if the child produced a name of an object present in the room; UL responses, if the child produced a word related to the last sentence; URL responses, if the child produced a word related both to an object in the room and to the last sentence; U responses, if the child produced a word semantically unrelated to the sentence, and not derived either from objects of the room or from previous sentences.

1 = if the child a word related to the sentence or to the related answer (S-type responses) These responses were subdivided into: SA responses, if the word given was semantically related to the sentence; SB responses, if the word given was semantically related to the completion of the sentence.

3 = if the child said a word which completed the sentence (C-type responses).

Thus, a high score in section B meant a poor performance (the maximum value is 30). Children were asked how they carried out the test when they had completed it.

c. Letter Fluency

Subjects had to produce as many words as possible, which began with a particular letter (c*, s, p*) within 60 seconds. No names of people, countries or towns were allowed. The number of words produced in each 15 seconds period was recorded.

7.2.2 Statistical analysis

A MANCOVA (Group was the main factor and Age covaried) was carried out on the variables of each task. The results are reported splitting the two groups in two age ranges: 7-8 years and 9-12 years. The decision to split the groups according to these age bands was related to the number of subjects in each subgroups and not for any other developmental theory on that.

7.2.3 Results

a. The Junior Brixton Spatial Rule Attainment Test

The results of the four groups of children at the Junior Brixton are reported in table 7.1.

Table 7.1

Results for the Junior Brixton (study 1)

Measures	ADHD 7-8 yrs. (n = 10) Mean (SD)	ADHD 9-12 yrs. (n = 21) Mean (SD)	Controls 7-8 yrs. (n = 16) Mean (SD)	Controls 9-12 yrs. (n = 17) Mean (SD)
Correct responses (max 40)	24.90 (6.21)	27.52 (4.41)	27.56 (3.50)	30.12 (2.89)
Perseverations	4.40 (2.07)	5.90 (3.16)	3.94 (2.49)	3.53 (1.74)
Plausible rules	5.70 (2.57)	4.10 (2.36)	5.38 (2.73)	4.88 (1.69)
Guessing responses	5.00 (3.86)	2.48 (2.06)	3.13 (2.06)	1.47 (1.59)

A MANCOVA was computed on the overall correct responses and on the three types of error of the Brixton Spatial Rule Attainment Test. For the number of correct responses, there were significant effects of both ADHD and of age [$F(1,63) = 6.212$, $p < .02$, $Eta^2 = 0.092$; $F(1,63) = 5.306$, $p < .05$, $Eta^2 = 0.080$, respectively]. For error type 1 (Perseverations), there was only a significant effect of ADHD [$F(1,63) = 6.543$; $p < .02$, $Eta^2 = 0.097$]. For error type 2 (Plausible rules) no significant effect was observed. For error type 3 (Guessing responses), there were significant effects of both ADHD and of age [$F(1,63) = 5.541$, $p < .05$, $Eta^2 = 0.083$], [$F(1,63) = 11.795$, $p < .01$, $Eta^2 = 0.162$] respectively.

b. The Junior Hayling Sentence Completion task

In order to reduce the possible number of comparisons (to avoid Type I errors) only two variables in Section A and four variables in Section B were included into the analysis. The two variables for Section A were: Accuracy and RTs of correct completion of sentences. The four variables for Section B were: Total Score (as described into Material section), C-type responses, S-type responses and [(UR+UL+URL)-U]-type responses, this latter variable represent the capacity to use a strategy (objects in the room and words related to the previous sentence) minus the non-strategic responses. The results of the Junior Hayling test are shown in table 7.2.

Table 7.2

Results for the Junior Hayling Sentence Completion task (study 1)

Measures	ADHD 7-8 yrs. (n = 10) Mean (SD)	ADHD 9-12 yrs. (n = 21) Mean (SD)	Controls 7-8 yrs. (n = 16) Mean (SD)	Controls 9-12 yrs. (n = 17) Mean (SD)
SECTION A				
Correct responses (max 10)	9.70 (0.67)	9.56 (0.36)	9.63 (0.62)	9.94 (0.24)
RT correct responses	1.07 (0.33)	0.89 (0.35)	0.69 (0.14)	0.55 (0.16)
SECTION B				
Score (max 30)	2.70 (2.36)	4.76 (2.21)	2.37 (2.06)	2.59 (1.70)
c-responses	0.10 (0.32)	0.14 (0.36)	0	0
s-responses	2.40 (1.65)	4.33 (1.93)	2.44 (2.13)	2.65 (1.62)
(ur+ul+url)-u	1.50 (4.22)	1.81 (3.72)	2.44 (4.07)	4.53 (2.79)

Note: Section A = Ss. must complete the sentences with the appropriate word. Section B = Ss. must complete the sentences with a word semantically unrelated to the sentence frame and to each word in it. c-responses = words that complete the sentence; s-responses = words semantically related to words in the sentence or related to the missing word; ur-responses = words semantically unrelated to the sentence frame and derived from an object present in the examination room; ul-responses = words semantically unrelated to the sentence frame and derived from a word given in the previous sentence; url = word semantically unrelated to the sentence frame but related both to an object present in the examination room and to the last sentence; u-responses = words semantically unrelated to the sentence and not derived from either an object present in the room or from the last sentence.

For section A, a MANCOVA (age covaried) was carried out on response speed and accuracy. For response speed, the effects of both ADHD and age were significant [$F(1,63) = 36.728$, $p < .001$, $Eta^2 = 0.207$; $F(1,63) = 15.961$, $p < .001$, $Eta^2 = 0.376$, respectively]. For accuracy, there was no significant effect. For section B, the same type of MANCOVA was carried out on the variables of the task: Total score, c-type responses (completion of sentence), s-type responses (words related to the sentence or to the missing word), and the difference between strategic (ur+ul+url) responses minus non-strategic (u) responses. [ur-type responses refer to names of objects in the room; ul-type responses refer to words related to the previous sentence; url-type responses have both proprieties; and u-type response refer to words unrelated to the sentence, but they are produced without using any strategy]. There was an ADHD effect on the Total Score

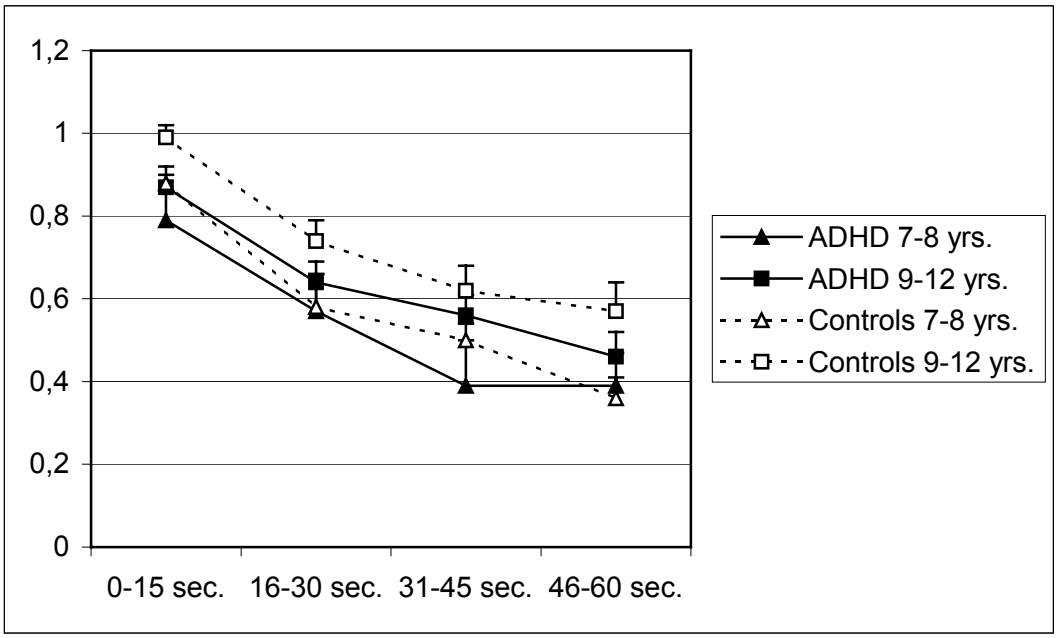
[F(1,63) = 7.445, p < .01, Eta^2 = 0.109], on c-type responses [F(1,63) = 4.588, p < .05, Eta^2 = 0.070], on s-type responses [F(1,63) = 4.449, p < .05, Eta^2 = 0.068] and on (ur+ul+url)-u responses [F(1,63) = 4.330, p < .05, Eta^2 = 0.066].

c. Letter Fluency

The results obtained in Letter Fluency task are shown in figure 7.1. A raw score of 0 was transformed into 0.50, and a log transformation was applied to normalize the variance.

Figure 7.1

Letter fluency results (study 1)



Note. Log. of number of words produced in four blocks of 15 seconds.

A 2 X 4 ANCOVA (ADHD X 4 Time blocks, Age covaried) was computed on the number of words produced by the children in one minute. The Age effect was significant [$F(1,61) = 6.750$, $p < .02$, $Eta^2 = .100$] but the ADHD effect was not significant [$F(1,61) = 2.421$, n.s., $Eta^2 = .038$]. Moreover, the effect of Time-block (of 15 seconds each) was significant [$F(3,61) = 9.964$, $p < .01$, $Eta^2 = .140$]. None of the interactions were significant.

7.2.4 Discussion

The Brixton, Hayling and Verbal Fluency tests had been selected because they had previously been shown to involve prefrontal functions in adult subjects (Burgess & Shallice, 1996a; 1996b; Stuss et al., 1998). Study 1 showed that on the Brixton Spatial Rule Attainment Test, the ADHD children performed more poorly than controls, as the frontal patients did in the study of Burgess & Shallice (1996b). However, ADHD children showed a difference from adult frontal patients on the pattern of errors. Frontal patients produced an excess of "Guessing" errors (error type 3), but not "Plausible rules" errors (error type 2) responses. However, ADHD children also

produced an excess of "Perseverative" errors (error type 1) on the test which frontal patients did not. As an excess of perseverative errors occurs in many other situations following frontal lesions, e.g. in memory retrieval (Stuss et al, 1994), as well as so-called stuck-in-set perseveration (Sandson & Albert, 1984), therefore the obtained ADHD effect on type 1 errors is not surprising. These errors can be interpreted as an even more basic "prefrontal" behaviour than that found in adult patients with prefrontal lesions which do not greatly affect overall IQ. There is though an interesting contrast between the results of the Junior Brixton and those of other studies which used the Wisconsin Card Sorting Test, where a significant difference between ADHD and normal controls on the percentage of perseverative errors was not found (Barkley et al., 1992; Grodzinsky & Diamond, 1992; Klorman et al., 1999; Reader et al., 1994; Pennington & Ozonoff, 1996).A possible explanation of the difference between this result on perseverative errors and what other authors found is that the two tasks (Junior Brixton and WCST) assess different cognitive skills. Firstly, the Junior Brixton requires subjects to abstract a spatial rule (movement of the turtle) instead of a specific perceptual category (color, form, number); secondly, the Junior Brixton does not require that a certain number of correct responses be produced the rule changes; thirdly the adult neuropsychology literature claims that the perseverative errors of the WCST are mostly observed in patients with right dorsolateral prefrontal cortex damage (Stuss et al., 2000), whereas perseverative errors in the Brixton are mainly observed in patients with left prefrontal cortex (Reverberi, Lavaroni, Gigli, Skrap and Shallice, 2005). Thus, it is necessary to analyse, more carefully, if the significant higher number of perseverative errors in children with ADHD could be due to the presence of children with a comorbid disorder (ADHD + RD) or if it is a generalized problem in children with ADHD.

Secondly, in the Hayling Sentence Completion Test (Burgess & Shallice, 1996a) children with ADHD performed more poorly because they were less able to produce words semantically unrelated and to do so they were less able than the controls to apply any strategy. One phenomenon found in prefrontal patients (e.g. Owen et al, 1990; Burgess & Shallice, 1996a; Shallice & Burgess,

1997) is a failure to develop or apply a strategy which normal subjects adopt to deal with a problem that occurs in carrying out a particular test. Thus in the Hayling Sentence Completion task, adult controls frequently come to adopt one of two strategies in order to produce a possible response before the sentence frame is given; when the sentence frame is actually presented, they then check that the putative response does not fit before producing it. The strategy used is most often the more concrete one of naming objects in the room; both measures of correct responses related to the room (ur, url) are given significantly more often by the normal control group than the ADHD group. Analysing the age subgroups within each sample it is necessary to underline that among the ADHD group, older children showed more problems in changing the semantic domain and producing *s*-type responses than did younger subjects ($p < .02$). In this group, instead, the older children were more sensitive to the semantic constraint of the sentences and they were less flexible, perhaps because they have had more experiences with these sentences during their life and this caused them to have more difficulties to separate out the last word from the rest of the sentence.

Why, on the other hand, would Letter Fluency be relatively spared? Responses in this test are short and can be independent of each other and speed is not a critical factor. Also it is possible that the left dorsolateral prefrontal systems which are activated in fluency tasks and where the primary deficit occurs in patients (Milner, 1963; Stuss et al, 1998; Frith, Friston & Frackowiak, 1991) are intact in children with ADHD. Overall the current results strongly support previous findings reviewed by Pennington and Ozonoff (1996) of the impairment of ADHD children on tests of Executive Functions. They support their metaanalysis of a relative sparing on one test – Letter Fluency – which does not show the characteristic pattern of left or medial prefrontal groups. Most importantly, the study extends this Executive Function deficits found in ADHD into the areas of strategy production and application and of error correction. The possibility is raised that the pattern of results can be explained by deficits to a high-level effort system related to Swanson & Posner et al's (1998) hyperactive impulsive network and to a right frontal vigilance system involved in monitoring.

7.3 Study 2

7.3.1 Aims of study 2

In study 1 a difference between ADHD and Controls was found concerning the production of semantically unrelated words of the Junior Hayling and of the detection of visuo-spatial rules of the Brixton, but the children with ADHD were not impaired on the Fluency task.

Study 2 was carried out in order to answer further questions. Firstly, in study 1 children with ADHD+RD were not separated from those with ADHD-only, therefore it was not possible to know if specific cognitive deficits could be due to the presence of ADHD or comorbidity (ADHD+RD). Secondly, it could also be interesting to analyze the type of perseverative errors on the Junior Brixton since there are different types of responses that have been classified as perseverations in study 1. Thirdly, the performance on the Junior Hayling could be analyzed in more detail, in particular the time of response of the correct and incorrect words in order to detect if the RTs could be a reliable index of the use of strategies. Finally, we were interested to inspect more carefully the performance on the Fluency by also task presenting a semantic fluency task in association with a letter fluency task.

As already mentioned, in study 2 the reading skills had been assessed in order to distinguish children with ADHD-only from those with ADHD + Reading Disorder; and also to include a second control group with pure Reading Disorder (RD-only). The choice of including a group of RD-only was motivated by several factors: the Brixton had been used in studies with ADHD, Reading Disabled (RD) children (Bayliss & Roodenrys, 2000) and with frontal damaged patients (Burgess & Shallice, 1996; Reverberi et al., 2002). As already mentioned in the introduction, Bayliss and Roodenrys (2000), who studied children with ADHD or RD presenting the standard version of the Brixton, found that only children with ADHD were impaired in this task, confirming the hypothesis that ADHD is characterized by an impairment to the Supervisory Attentional System (Norman & Shallice, 1986). Actually, from their report it is not clear if the ADHD group included

or not children with ADHD+RD, because reading performance was not reported although the Learning Problem Index of the Conner Rating Scale (Conners, 1969) was higher (indicating more severity) in the ADHD group (T = 86.21) than in the RD group (T = 80.00), therefore it is possible that the impairment of the children with ADHD could be confounded by the presence of children with comorbidity (ADHD + Reading Disorder).

7.3.2 Material

a. Junior Brixton Spatial Rule Attainment Test

In study 2, three different types of Perseverations have been considered. Starting from the original classification of errors according to Burgess and Shallice (1996b) (Perseverations – Error 1, Use of Plausible rules – Error 2, Guessing responses – Error 3), we analysed further types of perseverations, separating the errors due to: the incorrect use of the previous rule (Perseveration of Previous Rule - PPR), the reiterated production of the same response (Perseveration of Same Response - PSR) or the inappropriate use of the current stimulus (Perseveration of Same Stimulus - PSS). Using this classification of errors, it is possible to separate three types of perseverations according to the nature of the interfering stimuli: internal, own behaviour and external, respectively. The Perseveration of Rule could be due to the interference of a schema triggered by internal rules; the Perseveration of Stimulus could be due the interference of a schema triggered by external stimuli; and the Perseveration of Response could be to the interference of a schema triggered by own behaviour. Some responses could be coded as both Perseveration of Previous Rule and Perseveration of Same Response.

b. Junior Hayling Sentence Completion Test

In study 2, we were interested to analyse more deeply the RTs of the responses of section B. For this reason, three types of responses were recorded: c (completion), s (semantically related), u (unrelated), but also data on the speed of responses have been collected, separating the "correct"

responses (u) from the wrong ones (c and s). Our hypothesis is that children with ADHD are faster in giving the related words (c or s) and slower with the unrelated (u) word, for their impulsiveness to inhibit a wrong response (c or s) and their difficulty in using a strategy to find a word that does not fit with the sentence (u). We, therefore, calculate a variable that represent the speed of giving a correct responses that are related to the use of a strategy: RT (u-type response) – RT (c+s responses).

c. Verbal Fluency

The Verbal Fluency task was examined because most previous studies found differences between frontal patients and controls (e.g. Stuss et al., 1998). Verbal fluency measures can be further divided into Letter and Semantic fluency tasks. As in study 1, in Letter Fluency task subjects had to produce as many words as possible, which began with a particular letter (*c, s*) within 60 seconds. No names of people, countries or towns were allowed. Number of words produced every 15 seconds, and number of phonemic clusters (two words with identical second letter) were recorded. Moreover, in study 2 we administered also a Semantic Fluency task, because we were interested to analyse, if any, the difference between the Letter Fluency and the Verbal Fluency, since the former requires more frontal lobe activity and the latter more temporal lobe activity. For the Semantic Fluency task, subjects had to produce as many words as possible, which belonged to a specific category (*Sports, School tools*). The number of words produced every 15 seconds (total time was 60 seconds) was recorded.

7.3.3 Statistical analysis

In study 2 we were interested both to replicate the results obtained in study 1 and to analyse more deeply the effect of the presence of ADHD and / or RD on the Executive Function tasks. For this reason, each task was analysed running two sets of statistics:

1) A MANCOVA (age was partialled out) was conducted to check the findings reported on study 1. Related to this analysis, we reported the performance of all children with ADHD (ADHD-only and ADHD+RD) and the control group (excluding the RD condition), splitting the two groups in two subgroups according to their age as we did in study 1: ADHD 7–8 years (N = 26), ADHD 9-12 years (N = 29), NC 7-8 years (N = 9), NC 9-12 years (N = 28).
2) A 2 x 2 MANCOVA (ADHD by RD, age was covaried), was run in order to detect the effect on the performance due the presence of ADHD, RD or the interaction.
3) If an interaction ADHD by RD was present, comparisons between each clinical group to Controls were carried out (Alpha level was set at .05).

7.3.4 Results

a. The Junior Brixton Spatial Rule Attainment Test

The first analysis was run in order to assess whether the findings replicated the results of study 1 and for this reason we considered only the children with ADHD-only and ADHD+RD (defining them as simply ADHD). The first set of analysis was run considering the three types of errors according to the classification of Burgess and Shallice (1996b). The results of the Junior Brixton for ADHD and Controls, divided into two age groups, are reported in table 7.3a.

Table 7.3a

Results for the Junior Brixton (RD excluded; study 2) – Analysis I

Variables	ADHD 7-8 yrs. (n = 26)		ADHD 9-12 yrs. (n = 29)		Controls 7-8 yrs. (n = 9)		Controls 9-12 yrs. (n = 28)	
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Correct responses	28.04	(6.21)	29.03	(4.07)	27.43	(5.35)	30.54	(2.43)
Perseverations	5.12	(3.27)	4.59	(1.82)	4.86	(2.04)	2.86	(1.82)
Plausible Rules	3.96	(3.46)	4.07	(2.45)	4.87	(2.53)	4.48	(2.03)
Guessing Responses	2.88	(2.32)	2.38	(1.92)	2.63	(2.20)	2.15	(1.73)

A MANCOVA was performed on the original variables of the Junior Brixton (Group was the main effect, age was partialled out). The age effect was significant for Total Correct responses [$F(1,89) = 9.690$, $p < .01$, $Eta^2 = .101$], for Perseverations [$F(1,89) = 6.145$, $p < .02$, $Eta^2 = .067$], for Guessing responses [$F(1,89) = 6.580$, $p < .05$, $Eta^2 = .071$]. In addition, there was a trend toward an ADHD effect on Perseverations [$F(1,89) = 3.485$, $p < .07$, $Eta^2 = .039$]. Furthermore, a second type of analysis (analysis II) was carried out because it was interesting to separate out different types of Perseverations as described above. Results are reported on table 7.3b.

Table 7.3b

Results for the Junior Brixton (RD excluded; study 2) – Analysis II

Type of Perseverations	ADHD 7-8 yrs. (n = 26)		ADHD 9-12 yrs. (n = 29)		Controls 7-8 yrs. (n = 9)		Controls 9-12 yrs. (n = 28)	
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
PPR	3.04	(2.09)	2.24	(1.75)	2.71	(1.80)	1.61	(1.37)
PSR	0.72	(0.94)	0.86	(0.83)	1.00	(0.58)	0.75	(0.89)
PSS	1.32	(1.49)	1.34	(1.40)	1.14	(1.46)	0.39	(0.63)
PPR-PSR	0.04	(0.20)	0.14	(0.35)	0	(0)	0.11	(0.31)

Legend: PPR = Perseveration of Previous Rule, PSR = Perseveration of Same Response, PSS = Perseveration of Same Stimulus. Note: Values are corrected by age.

On analysis II the age effect was significant for Perseveration – Previous Rule [$F(1,89) = 8.508$, $p < .01$, $Eta^2 = .090$]; the ADHD effect was significant only for Perseveration – Same Stimulus because ADHD children reiterated to point to the green turtle seen on the card, instead of trying to figure out a rule [$F(1,89) = 5.830$; $p < .02$, $Eta^2 = .063$].

Secondly, we considered RD status as well. In table 7.4a the results of the four groups (ADHD-only, RD-only, ADHD+RD and Controls) are reported considering the error scoring criteria used in Study 1 (Analysis I).

Table 7.4a

Results for the Junior Brixton (RD included; study 2) - Analysis I

	ADHD-only (n = 38)		RD-only (n = 39)		ADHD+RD (n = 17)		Controls (n = 37)	
Variables	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Correct responses	30.32	(4.04)	29.76	(2.96)	26.70	(6.71)	29.50	(3.36)
Perseverations	4.47	(2.37)	4.00	(2.50)	4.75	(3.50)	3.43	(2.39)
Plausible Rules	3.29	(2.45)	4.12	(2.75)	5.13	(3.64)	4.68	(2.12)
Guessing Responses	1.97	(1.54)	2.12	(1.81)	3.42	(2.90)	2.39	(1.82)

On all variables of the Junior Brixton a 2 x 2 MANCOVA (ADHD x RD, age was partialled out) was performed. As far as the analysis I is concerned the age effect was significant for: Total Correct Responses [$F (1,121) = 15.357$, $p < .001$, $Eta^2 = .116$]; and Perseverations [$F (1,121) = 7.065$, $p < .01$, $Eta^2 = .057$]. The ADHD effect approached significance for Perseverations [$F (1,121) = 3.530$, $p < .07$, $Eta^2 = .029$]; and the RD effect was significant for Total Correct Responses [$F (1,121) = 5.166$, $p < .05$, $Eta^2 = .042$]. More interestingly the interaction ADHD by RD was significant for the following variables: Total Correct responses [$F (1,121) = 6.958$, $p < .01$, $Eta^2 = .056$], Plausible rules [$F (1,121) = 5.720$, $p < .02$, $Eta^2 = .047$], and Guessing responses [$F (1,121) = 6.997$, $p < .01$, $Eta^2 = .056$].

Given the significant interactions between ADHD and RD we tested which clinical group performed significantly more poorly than Controls. The difference between ADHD+RD and Controls was significant ($p = .019$) on Total Correct Responses and on Guessing Responses ($p = .032$). Furthermore, a second type of analysis (analysis II) was carried out to separate out different types of Perseverations as described above and considering also children with RD. The results are reported on table 7.4b.

Table 7.4b

Results for the Junior Brixton (RD included; study 2) - Analysis II

	ADHD-only (n = 38)		RD-only (n = 39)		ADHD+RD (n = 17)		Controls (n = 37)	
Variables	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
PPR	2.24	(1.64)	2.49	(1.73)	2.65	(2.43)	1.98	(1.65)
PSR	0.76	(0.86)	0.62	(0.91)	0.95	(1.28)	0.79	(0.87)
PSS	1.33	(1.22)	0.88	(1.29)	1.15	(1.81)	0.58	(1.23)
PPR-PSR	0.15	(0.26)	0.02	(0.28)	0	0	0.08	(0.27)

Legend: PPR = Perseveration of Previous Rule, PSR = Perseveration of Same Response, PSS = Perseveration of Same Stimulus. Note: Values are corrected by age.

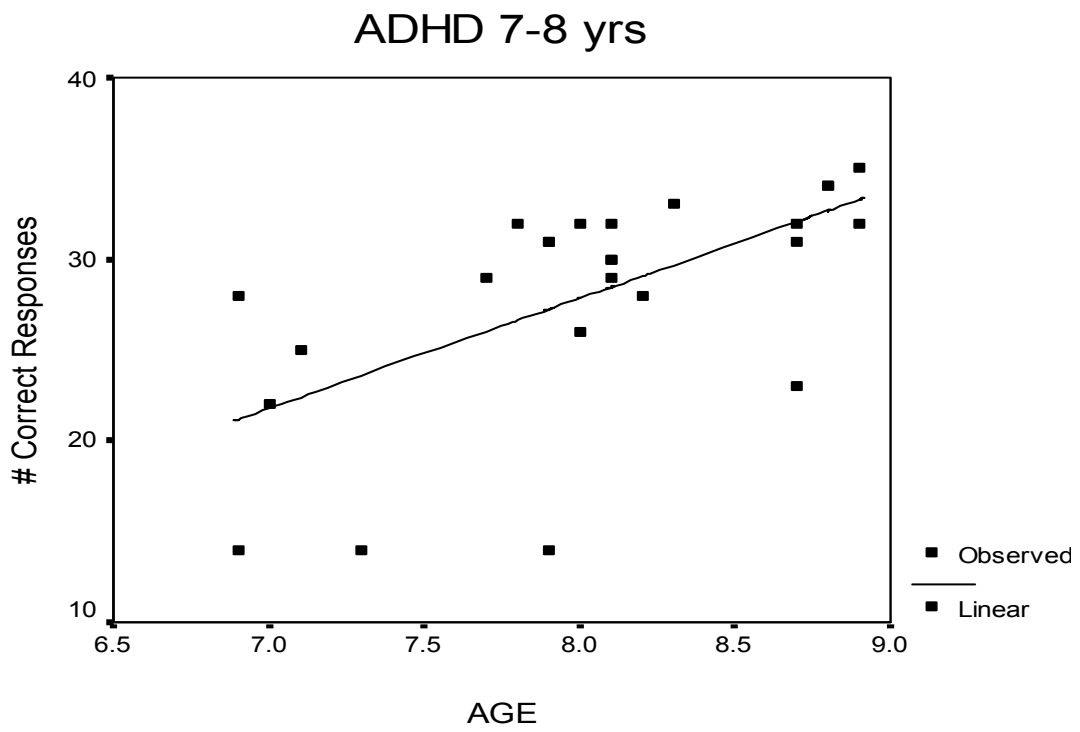
As far as the analysis II is concerned the age effect was significant for Perseveration - Previous Rule [$F(1,121) = 11.820$, $p < .001$, $Eta^2 = .092$]: younger children performed significantly more poorly than the older children. The only significant effect due to the presence of ADHD was on Perseveration - Same Stimulus [$F(1,121) = 4.208$, $p < .05$, $Eta^2 = .035$].

In order to investigate lack of replication of the effect of ADHD, in figure 7.1 the number of Total Correct responses produced in study 2 by ADHD-only, ADHD+RD aged 7-8 years, is reported.

Figure 7.1

Total Correct Responses on Junior Brixton

produced by all ADHD children aged 7-8 yrs in study 2



The regression analysis performed on the Total Correct responses by Age selecting only ADHD children aged 7-8 years old revealed a significant linear effect [$R^2 = .47$, $F(2, 28) = 12.42$, $p < .001$].

Since the age of the ADHD children of the 7-8 years sub-group was significantly different in the two studies [Study 1 = 7.62 (0.50) vs. Study 2 = 8.19 (0.67) [$t(65) = 3.80$, $p < .001$], the sample of study 2 was larger and the age effect was also present in study 1, we suppose that the partial lack of replication of study 1 may be due to the presence of more older ADHD children in the subgroup of 7-8 years in study 2 than in study 1. The older ADHD children would be expected to have fewer problems in the Junior Brixton (since there is a significant Age effect also in the ADHD 7-8 years group).

b. Junior Hayling Sentence Completion Test

For the Junior Hayling the same analysis described above were carried out considering the same variables of study 1, but also including a new variable in order to assess the speed of responses in the section B. This new variable was obtained from the difference of RTs of *u*-type responses minus the RTs of *c+s*–type responses. This variable is held to reflect a measure of mastery of using a strategy, because it is postulated that, if a subject is using a strategy s/he can give faster *u*-type responses and slower *c* or *s* – type responses. The results of the Junior Hayling, without considering the RD status, are reported in table 7.5.

Table 7.5

Results for the Junior Hayling (RD excluded; study 2)

Measures	ADHD 7-8 yrs. (n = 26)		ADHD 9-12 yrs. (n = 29)		Controls 7-8 yrs. (n = 9)		Controls 9-12 yrs. (n = 28)	
SECTION A	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Correct responses	9.40	(0.91)	9.45	(0.69)	9.44	(0.57)	9.61	(0.73)
RT correct responses	0.87	(0.26)	0.65	(0.22)	0.86	(0.30)	0.62	(0.25)
SECTION B								
Total Score	3.48	(1.85)	3.48	(1.98)	2.56	(1.59)	2.93	(1.88)
c-responses	0.04	(0.20)	0.14	(0.35)	0	0	0.04	(0.19)
s-responses	3.40	(1.80)	3.07	(1.75)	2.56	(1.59)	2.86	(1.86)
(ur+ul+url)-u	1.12	(4.13)	2.07	(3.98)	-0.56	(4.90)	2.11	(3.39)
RT u-(c+s) resp.	1.96	(2.61)	0.55	(1.92)	-1.16	(2.54)	0.53	(1.61)

Note: Section A = Ss. must complete the sentences with the appropriate word. Section B = Ss. must complete the sentences with a word semantically unrelated to the sentence frame and to each word in it. C-responses = words that complete the sentence; S-responses = words semantically related to words in the sentence or related to the missing word; UR-responses = words semantically unrelated to the sentence frame and derived from an object present in the examination room; UL-responses = words semantically unrelated to the sentence frame and derived from a word given in the previous sentence; URL = word semantically unrelated to the sentence frame but related both to an object present in the examination room and to the last sentence; U-responses = words semantically unrelated to the sentence and not derived from either an object present in the room or from the last sentence.

A MANCOVA (Group was the main factor and age was partialled out) was performed on all variables of the Junior Hayling. On section A, there was only an age effect on RTs of correct completion of sentences [F (1,85) = 21.469, p <.001, Eta^2 = .207]. The effect of ADHD approached significance for Total Score in section B [F (1,85) = 3.634, p = .06, Eta^2 = .042], and it was significant for the new variable that evaluates the speed of using a strategy (RTs of *u*-type responses – RTs of (*c+s)* – type responses) [F (1,85) = 4.466, p < .05, Eta^2 = .052].

The second set of analysis was run including the RD status: the performance on the Junior Hayling by the four groups of study 2 was analysed; results are reported on table 7.6.

Table 7.6

Results for the Junior Hayling (RD included; study 2)

Measures	ADHD-only (n = 38)		RD-only (n = 39)		ADHD+RD (n = 17)		Controls (n = 37)	
SECTION A	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Correct responses	9.56	(0.66)	9.52	(0.64)	9.35	(0.65)	9.34	(0.64)
RT correct responses	0.72	(0.26)	0.78	(0.26)	0.67	(0.26)	0.70	(0.26)
SECTION B								
Total Score	3.77	(1.99)	2.64	(1.94)	3.01	(1.96)	2.72	(1.94)
c-responses	0.11	(0.29)	0.13	(0.28)	0.06	(0.28)	0.03	(0.28)
s-responses	3.44	(1.81)	2.40	(2.05)	2.76	(1.61)	2.78	(1.78)
(ur+ul+url)-u	1.21	(3.42)	1.54	(4.63)	3.22	(6.04)	1.38	(3.91)
RT u-(c+s) resp.	1.29	(2.15)	0.48	(2.23)	1.09	(2.22)	0.14	(2.15)

Note: Section A = Ss. must complete the sentences with the appropriate word. Section B = Ss. must complete the sentences with a word semantically unrelated to the sentence frame and to each word in it. C-responses = words that complete the sentence; S-responses = words semantically related to words in the sentence or related to the missing word; UR-responses = words semantically unrelated to the sentence frame and derived from an object present in the examination room; UL-responses = words semantically unrelated to the sentence frame and derived from a word given in the previous sentence; URL = word semantically unrelated to the sentence frame but related both to an object present in the examination room and to the last sentence; U-responses = words semantically unrelated to the sentence and not derived from either an object present in the room or from the last sentence.

A 2 x 2 MANCOVA (ADHD X RD, age was covaried) was run on all dependent variables of the Junior Hayling. For section A there was a significant effect of age on Correct responses [F (1,129) = 6.694, $p < .05$, $Eta^2 = .051$] and on RTs of correct responses [F (1,129) = 22.122, $p < .001$, $Eta^2 = .150$]. For section B, there an ADHD effect was significant only for the variable which reflects the speed of giving a correct response [F (1,129) = 4.021, $p < .05$, $Eta^2 = .034$]. The ADHD effect on the Total Score of Section B was not significant [F (1,129) = 2.578, $p = .11$, $Eta^2 = .020$]. There was no significant effect due to the presence of RD.

Concerning the use of strategies there was a significant difference between ADHD-only and ADHD+RD: children with ADHD+RD were more strategic than children with ADHD-only because they used the objects in the room more frequently than the children with ADHD-only [F(1,54) = 3.372, $p < .06$, $Eta^2 = .068$].

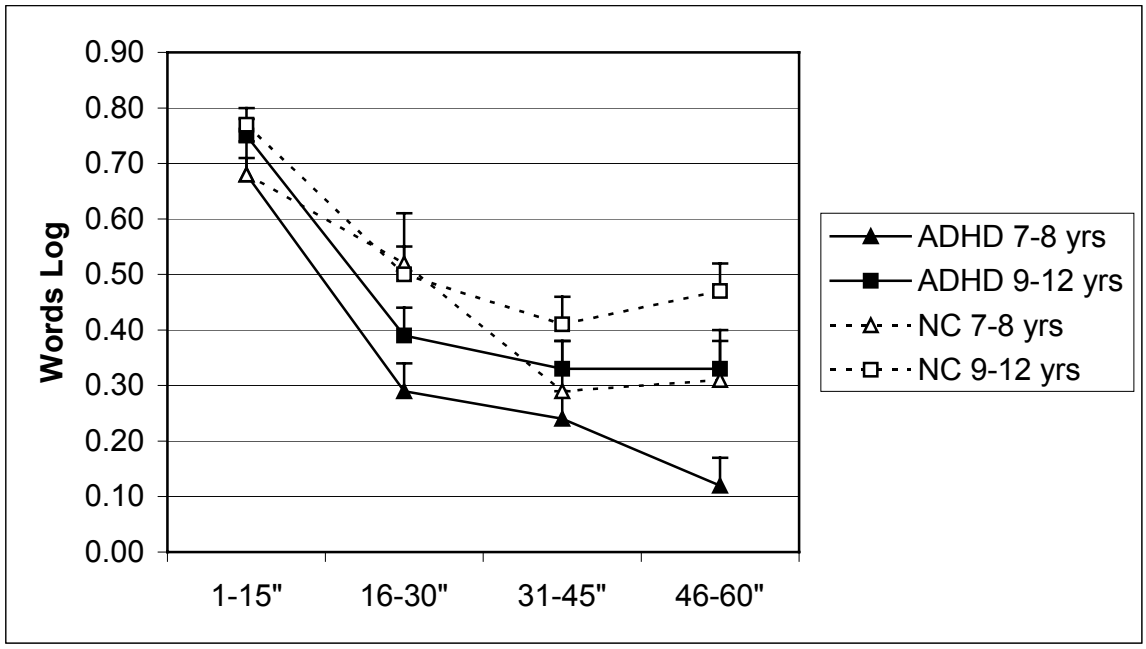
c. Verbal Fluency

The two Verbal Fluency tasks (Letter and Semantic) were analysed according to the same statistics described into study 1. A raw score of 0 was transformed into 0.5 and a log transformation was applied to normalize the variance.

For Letter Fluency a 2 x 4 ANCOVA (ADHD x 4 Time block, Age was partialled out) was computed on the number of words produced by the children in one minute. The results for Letter Fluency task are reported in figure 7.2.

Figure 7.2

Letter fluency results (RD excluded; study 2)

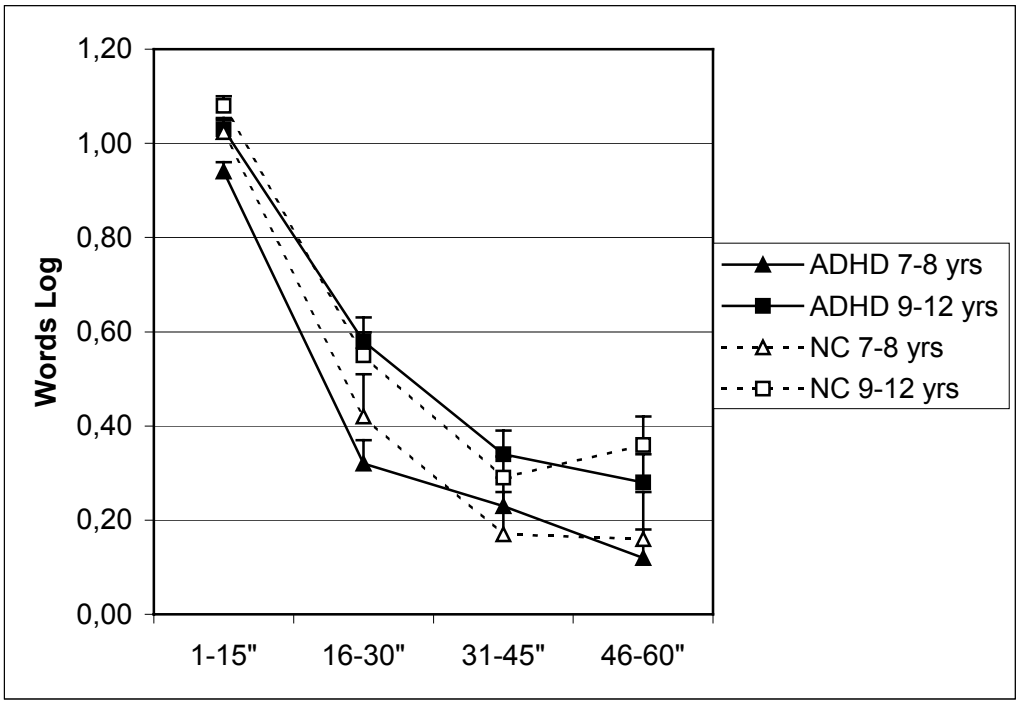


As in study 1 the effects of Age and of the Time block were significant: [$F(1,88) = 17.020$, $p < .001$, $Eta^2 = .161$], [$F(1,88) = 18.601$, $p < .001$, $Eta^2 = .173$], respectively. Moreover, the effect of ADHD was significant as well [$F(1,88) = 4.590$, $p < .05$, $Eta^2 = .049$]. All the interactions were not significant.

For the Semantic Fluency the same 2 x 4 ANCOVA was carried out. The results for Semantic Fluency of ADHD and Normal Control children are reported in figure 7.3.

Figure 7.3

Semantic Fluency results (RD excluded; study 2)

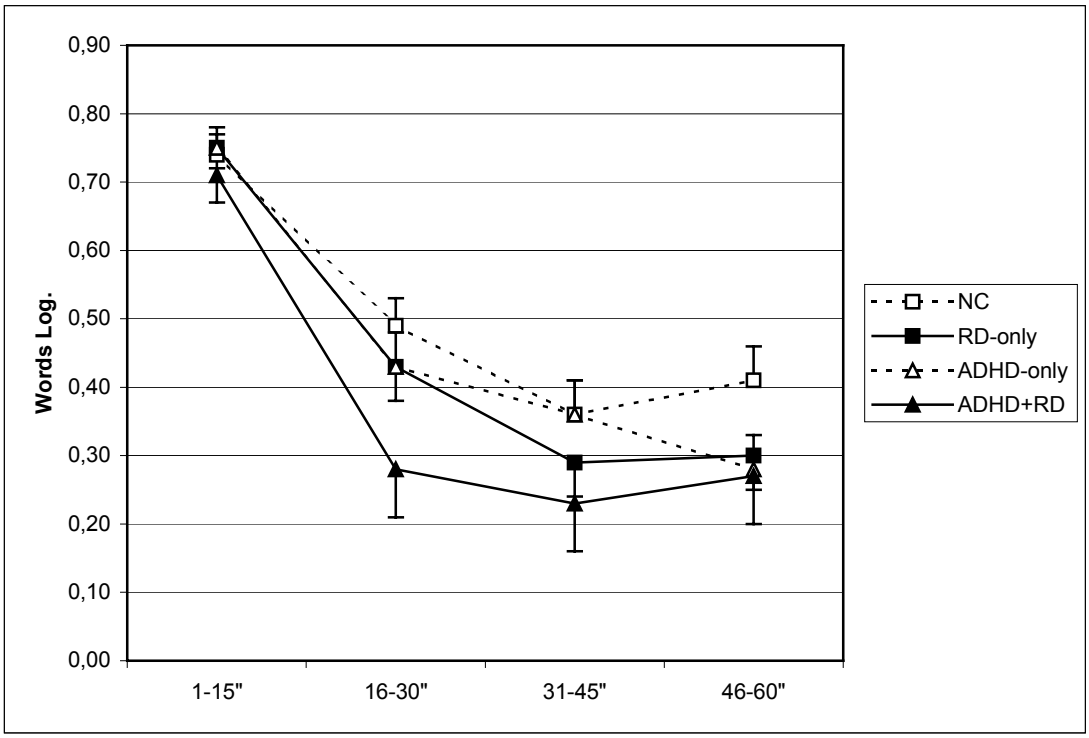


Again, the Age and the Time block effects were both significant: respectively [$F(1,88) = 29.260$, $p < .001$, $Eta^2 = .247$] and [$F(1,88) = 15.515$, $p < .001$, $Eta^2 = .148$]. The ADHD effect and the interactions were not significant.

The second set of analysis concerning Verbal Fluency was run including also the group of children with RD-only and splitting children with ADHD in two groups: ADHD-only and ADHD+RD. The results concerning Letter Fluency are reported in figure 7.4.

Figure 7.4

Letter fluency results (RD included; study 2)



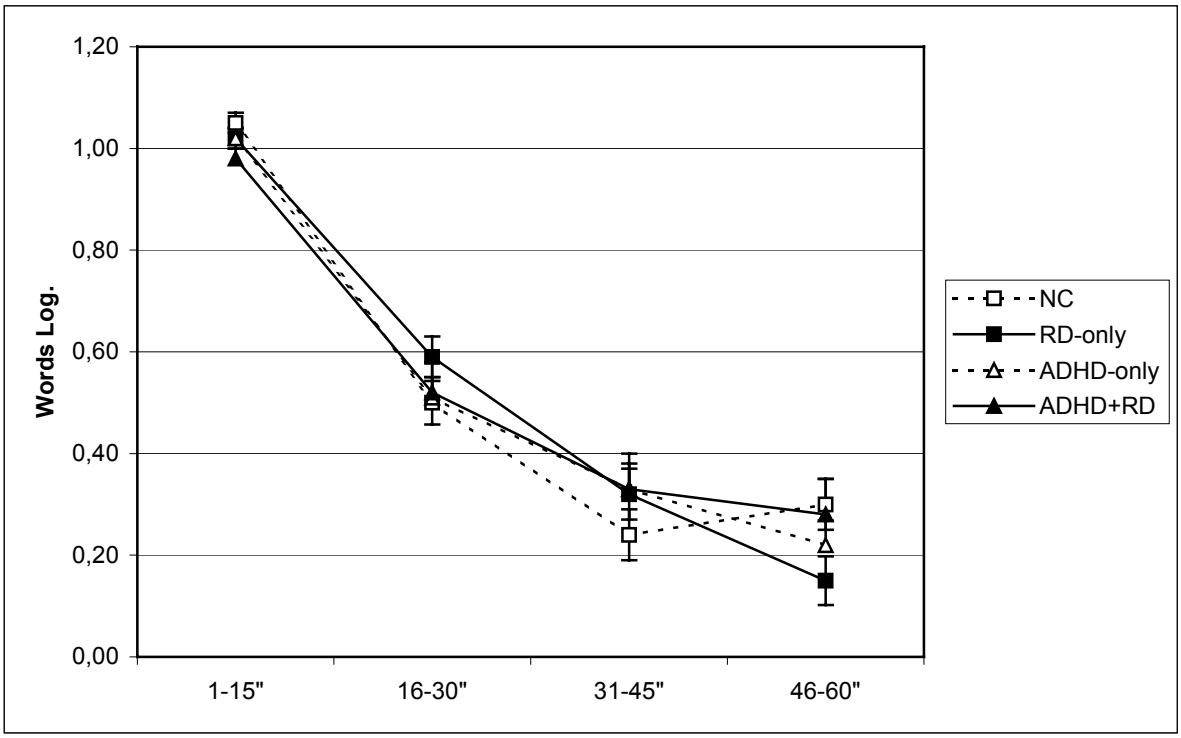
Note. Values are corrected by age and reported in log, semi-bars are standard errors.

Two 2 x 2 x 4 ANCOVAs (ADHD x RD x Time-Blocks) were run on the number of words produced for Letter and Semantic Fluency tasks. As far as Letter Fluency is concerned the Time block [$F(1,124) = 17.130$, $p < .001$, $Eta^2 = .121$] and the Age effects [$F(1,124) = 25.232$, $p < .001$, $Eta^2 = .169$] were significant. Moreover the RD effect was significant [$F(1,124) = 5.200$, $p < .05$, $Eta^2 = .040$] and the ADHD effect was not significant [$F(1,124) = 3.052$, $p = .062$, $Eta^2 = .024$]. The interactions were not significant.

The results for the Semantic Fluency task are reported on figure 7.5.

Figure 7.5

Semantic Fluency results (RD included; study 2)



Note. Values are corrected by age and reported in log, semi-bars are standard errors.

The same 2 x 2 x 4 ANCOVA (ADHD by RD by Time-block, age covaried) was performed on the Semantic Fluency task. The Age effect [$F(1,124) = 30.478$, $p<.001$, $Eta^2 = .197$] and the Time block effect [$F(1,124) = 22.024$, $p < .001$, $Eta^2 = .151$] were both significant, but neither the ADHD [$F(1,124) = 0.002$, n.s.] nor the RD [$F(1,124) = 0.021$, n.s.] effects were significant. The interactions were not significant.

7.3.5 Discussion of study 2

The aims of these two studies were to analyse the prefrontal – executive functioning of children with ADHD and / or Reading Disorder. The ADHD group was selected because an increasing number of papers showed the impairments of these children in tests measuring prefrontal functioning (for a review, Pennington & Ozonoff, 1996; Sergeant et al., 2002; Willcutt et al., 2005). The group of children with ADHD+RD and with RD-only were selected for three reasons: 1) the

frequent comorbidity between the two disorders (Welsh & Pennington, 1993), 2) the debate on the specificity and differences between the patients with ADHD+RD and Dyslexia (Frith, 1999), 3) and the possible presence of Executive Dysfunctions in children with Dyslexia (Brosnam et al., 2002).

In study 2 there are three main differences with respect to study 1, in the method, that are worth being underlined: 1) children were presented with reading tests in order to separate out the ADHD-only children from those with ADHD + Reading Disorder; 2) a group of children with specific Reading Disorder (RD-only) were included in order to contrast their prefrontal skills with those of children with ADHD-only or ADHD+RD; 3) the four groups were not matched for age, and for this reason analysis covariating with age were used.

(i) Junior Brixton

As far as the Junior Brixton is concerned in study 2 a complete replication of the ADHD on the Total number of correct responses was not obtained. The possible reason of this partial lack of replication could be found into the relation between Total Correct Responses and age. In both studies the age effect was significant and in particular as shown in Figure 7.1 there is a linear effect of age in study 2 on the performance of Junior Brixton in the ADHD group aged 7-8 years. In study 2 the group of ADHD children aged 7-8 years were older than in study 1. This difference in the sample characteristics may have caused the partial lack of replication from study 1 to study 2.

However, considering the three types of errors proposed by Burgess and Shallice (1996b) (Analysis I), there was a trend of ADHD effect on errors due to Perseverative responses ($p < .07$). In study 2, a further differentiation of Perseverative errors was considered (Analysis II). Subjects made Perseverative errors if: 1) they used the previous (but no longer correct) rules to guess the movements of the turtle (Previous Rule); 2) they gave the same responses when inappropriate (Same Response); 3) they pointed to the current position of the green turtle (Same Stimulus). This type of differentiation was applied in order to distinguish perseverative errors due to: a cognitive schema that was erroneously active (Previous Rule); a behaviorally incorrect response schema not

mediated by environmental stimuli (Same Response); an incorrect activation of behavioral schema due the mediation of environmental stimuli (Same Stimulus).

Considering the different type of Perseverations (Analysis II) there was an ADHD effect for Perseverations - Same Stimulus: because children with ADHD tended to point to the green turtle seen on the card instead of trying to figure out where the turtle could move on the next card according to a particular rule. It is possible that the groups with ADHD made more Perseverations - Same Stimulus errors due to a sort of "capture behaviors". This result has been interpreted in terms of a difficulty to shift from a schema triggered by the environment due to an impairment of the Supervisory Attentional System (Norman & Shallice, 1986).

The second set of data analysis was run including also children with RD and considering four groups of children: ADHD-only, RD-only, ADHD+RD and Controls. Including children with RD-only and separating the two groups of children with ADHD a significant RD effect was obtained on Total Correct Responses (Analysis I), but not on the three types of errors separately. The ADHD by RD interaction on the Total Correct responses appeared to be due to a poorer performance of the ADHD+RD group compared to controls ($p = .019$). Since it was found a mild ADHD+RD impairment in the Junior Brixton it is possible that children with ADHD+RD present a dysfunction in the anterior region of the brain, as Burgess and Shallice (1996b), in particular in the left side (Reverberi et al., 2005), but this impairment was not present in children with ADHD-only. Moreover, as Reverberi et al. (2005) suggested the highest number of perseverative errors in left prefrontal patients were related to the Same Responses: therefore the hypothesis is that the Junior Brixton was not particularly sensitive for ADHD because, in particular children with ADHD+RD may present a dysfunction in left prefrontal cortex and this may causes an excessive number of perseverative errors due to the same incorrect responses.

(ii) Junior Hayling

Firstly, a partial replication of the result obtained in Study 1 concerning Total Score of Section B (Response Inhibition) was obtained in Study 2 (the effect of ADHD was $p = .06$), but considering the RD status of the children the trend of the ADHD effect disappeared.

However, if the RT of correct responses minus RT of incorrect responses, in Section B, was considered other interesting results have been obtained. The effect of ADHD was found to be significant, because children with ADHD were relatively slower in giving correct responses (and relatively faster to give incorrect responses) in Section B. This result could be interpreted in terms of difficulties to use a strategy by children with ADHD because they spent more time to produce a correct response than the other groups of children and they were not able to withhold an incorrect one.

(iii) Verbal Fluency

The third task analysed in this chapter was Verbal Fluency, namely the Letter and Semantic Fluency tasks. As far as the Letter Fluency is concerned, the age and time-block effects have been replicated in study 2. Moreover, the absence of an ADHD effect was replicated in study 2. Therefore, sparing on the verbal fluency task in children with ADHD is also confirmed by the second study. Sergeant et al (2002) in their meta-analysis of EF impairments in children with ADHD found that 6 out of 9 studies were able to discriminate ADHD from controls, but they suggested that, many studies did not control for IQ and the presence of Learning Disabilities. Actually, if the group with RD-only, which might also be expected to be impaired on fluency tasks, was excluded from the analysis, an ADHD effect was significant ($F(1,106) = 6.292$, $p = .014$). Moreover, it should be noted that the group with ADHD+RD was significantly poorer than Controls on the Letter Fluency tasks ($p = .019$). As this result is not strong, perhaps because of the small sample size, it would be useful to run other studies on this group of ADHD+RD children on the Letter Fluency task because it is possible that children with ADHD+RD may have an impairment in the left prefrontal cortex, as also

postulated from the analysis run on the Junior Brixton; indeed Stuss et al (1998) found that patients with left and middle prefrontal lesions performed significantly worse than patients with right and posterior lesions on Verbal Fluency.

In conclusion, on the Letter Fluency task (not the Semantic Fluency task), only children with ADHD+RD are be impaired, but not children with ADHD-only. For this reason, previous studies that did not separate children with ADHD-only from ADHD+RD found an ADHD effect on the Letter Fluency task possibly, because there was an artefact due to the presence of children with ADHD+RD.

7.4 General Discussion

(i) Junior Brixton

In study 2 the most relevant result concerns the interaction between ADHD and RD. The interaction was due to the worst performance of the group with ADHD+RD. In particular, the poorer performance of the group with ADHD+RD compared to ADHD-only was due to the higher number of Guessing errors ($p < .001$).

Actually, considering the ADHD by RD ANOVA there was a trend of ADHD effect concerning Perseverative errors ($p < .07$). This result shows that perseverative behavior could be a mild characteristic of children with ADHD.

Actually it is necessary to perform other studies using the Brixton task because it has not been clarified if children with ADHD present a true problem of attainment of spatial rules, in particular those with ADHD+RD, and if in general children with ADHD make more perseverative errors. Perhaps the use of the standard version of the task, more difficult than the current version, would transform this trend of effect in a significant effect. Moreover the ADHD+RD group was small ($N = 17$) and their impairment needs to be replicated with other studies using larger samples.

(ii) Junior Hayling

The second task used to replicate study 1 was the Junior Hayling. In study 1 the older ADHD children performed worse (considering Total Score of Section B) than the younger ADHD because they had more difficulties to inhibit an “automatic” completion of sentence and to find out a word sema word semce. Possibly, ttasgroupce aHD d5401T4001552 Tseej Tc 0.0648 Tw 12159

the areas found to be involved in the execution of the Hayling task could well be different from the regions involved in the execution of a short and auditory version of the Hayling task. Secondly, the performance of adults on the Hayling task may involve areas that are different from those activated by young children who have not completed yet their brain specialization, as has also been demonstrated for Verbal Fluency task.

(iii) Verbal Fluency

As far as the Verbal Fluency is concerned, it has been clarified that the mild ADHD effect actually found in the literature (Pennington & Ozonoff, 1996) could be due the inappropriate utilization of a group of ADHD children whose possible RD diagnosis was not controlled for; in fact in our studies the effect of ADHD was mild both in study 1 and in study 2, if the RD deficit was not partialled out. However, the ADHD effect completely disappeared when the Reading Disorder diagnosis was included into the analysis.

In summary, all children with ADHD were found to be impaired on the execution of the Junior Hayling, in particular in producing rapid and strategic semantically unrelated words; children with ADHD+RD were more impaired in the Junior Brixton, and the Verbal Fluency tasks did not differentiated the four groups.

Chapter 8

Attentional and rapid naming skills in children with ADHD and / or RD

8.1 Introduction

One of the most important cognitive domains that must be analyzed in ADHD and RD children is Attention. The nature and the extend of the purported attentional deficit in dyslexia therefore remain unclear. Posner & Petersen (1990) offered a theory of attention based on the working hypothesis that distinct neural networks accomplish component processes of alerting, orienting, and executive control. *Alerting* consists of suppressing background neural noise (by inhibiting ongoing or irrelevant activity and mental effort to establish a state of vigilance) to establish readiness to react. *Orienting* consist of mobilizing specific neural resources to prepare to process an expected type of input. *Executive control* consists of coordinating multiple specialized neural processes to direct behavior toward a goal. Posner and Raichle (1994) proposed that three neural networks (Alerting, Orienting and Executive Control) are localized on specific regions of the cortex: right dorsolateral prefrontal cortex, anterior cingulate and posterior parietal lobe respectively. The alerting processes and right frontal network operate to establish *sustained attention*; the orienting and posterior parietal network operate to establish *selective attention*; the executive control and anterior cingulate network operate to establish *divided attention.*

Using the theory proposed by Posner and Petersen (1990) Swanson et al. (1998) showed that children with ADHD are mainly impaired in the alerting and in the executive control systems, which lead to the hypothesis of neuropsychological dysfunction in the Anterior Cingulate, Supplementary Motor Are, Right Prefrontal Cortex, Globus Pallidus and Caudate Nuclei. The orienting system, according to Swanson et al. (1998), is spared in children with ADHD. Other details about the theory proposed by Swanson et al (1998) are reported on chapter 1.

The aim of this study is to investigate the attention functioning of children with ADHD or RD (or both) in tasks loading on components of the Posner & Petersen model (1990). Moreover, we

investigated if children with ADHD and / or RD present deficits in a rapid naming task as suggested by Tannock et al (2002).

The Alerting System has been assessed by two tasks based on the Sustained Attention Response Task (SART) proposed by Robertson et al. (1997). In the SART the subjects must name all digits appearing on the screen at a constant rate except for a particular digit (e.g. 3) which occurs at random about 1 every nine trials. This has however strong inhibition as well as sustained attention aspects, therefore we considered the response speed (as the readiness to respond) and the omission errors (as the ability to control lapses of attention) the two measures of the functioning of the Alerting System. We therefore added a second complementary test (called Vigilance task) where the subject must respond to only one target digit when it appears, and ignore the rest. This was intended to have equivalent sustained attention aspects but not to loan on inhibition because we consider the inhibition component as part of the Executive Control network. Moreover, the Executive Control network was assessed via a Stroop task which has been shown to be impaired in ADHD children on a number of occasions (Gorenstein et al, 1989; Boucugnani & Jones, 1989; Grodzinsky & Diamond, 1992). The subject must count the number of examples of a digit on the screen, which contains only one type of digit (e.g. four 3s). Perceptual and visuo-spatial functioning were assessed in two different ways: in study 1 a Silhouettes Test of the Visual Object and Space Perception Battery (VOSP; Warrington & James, 1991) was administered, which is derived from the Unconventional Views Test. In study 2, the Orienting System has been assessed through the Rotated Blackboard Test, an experimental mental rotation task (see materials for details).

For summarizing, the questions of the current study are the following:

1) Which Attentional network, according to the theory of Posner and Petersen, is impaired in children with ADHD, ADHD+RD or RD?
2) Do object rapid naming task differentiate children with RD from normal controls and from ADHD? What about children with ADHD+RD?

3) What is the nature of the attention deficits of the children with ADHD+RD? Are they more similar to ADHD or to RD?

8.2 Study 1

8.2.1 Material

a. Sustained Attention Response Task (SART)

The children were presented with 360 digits in two 7-minute sessions, with a pause of 1 minute between them. Digits were presented on a screen (14") at 0.70 cm. distance. The inter-stimulus interval (ISI) was 1 sec. and the stimulus disappeared when the child named the digit, or after 1 second. The children were asked to name all the numerals presented on the screen except for the target (in one session the target was "3" and in the other was "7"). The order of sessions was counterbalanced. RTs of correct responses were recorded, as well as the number of omission errors (when a non-target numeral was not named), and the number of commission errors (when a target numeral was named).

b. Vigilance Task

The stimuli and procedure were the same as in the previous experiment except for the task: participants were asked to name only the target (in one session the target was "2" and in the other it was "6").

c. Number Stroop task

In this test children were required to name or to count numbers. The trials were divided into two sessions each having 48 sets of numerals. The sets were composed from two to seven identical digits. In the first session, the task was to name the digits presented on the screen (just once, as they were all the same). In the second session, the task was to count the number of digits. The number of naming errors (the child naming the numbers instead of counting them) was recorded, as well as the

number of counting errors (a failure to count the digits in the set). Counting and naming RTs were recorded.

d. Modified Silhouettes Test

To assess the children's right infero-temporal functioning (Brincat & Connor, 2004), a shortened version of the Silhouettes Test (from VOSP; Warrington & James, 1991) was presented. Ten silhouettes of animals and 10 of objects were selected after a pilot study. The silhouettes of animals and objects were each presented individually by the examiner on a single card. The task was to name them. Scores ranged from 0 to 20.

8.2.2 Statistical analysis

For all measure a MANCOVA (ADHD as main factor, age covaried) was carried out. The age factor was considered in order to detect also a developmental trend for the two groups. The results are reported splitting the two groups in two age ranges: 7-8 years and 9-12. The decision to split the groups according to these ages was related only to the number of subjects in each subgroups.

8.2.3 Results

a. Sustained Attention Response Task (SART)

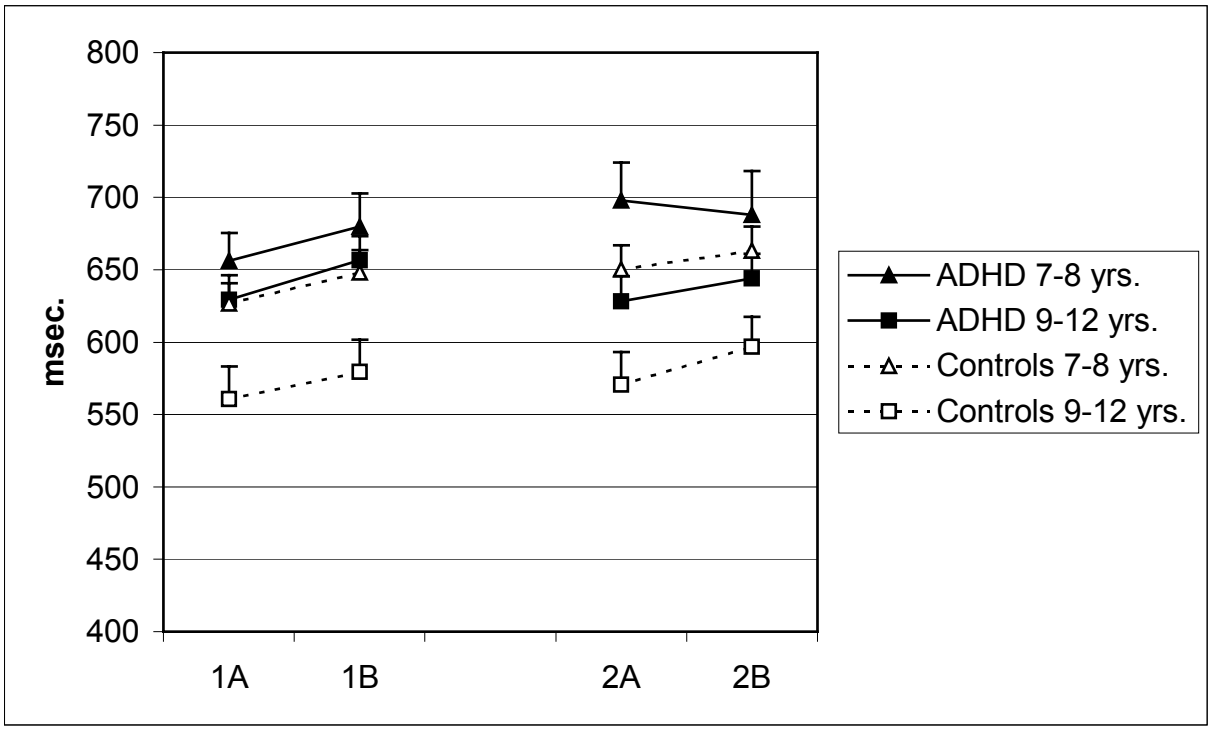
Three sets of 2 x 2 x 2 ANCOVAs (ADHD x Session x Block, age was covaried) have been calculated on median correct responses RTs, omission errors and commission errors. In addition, a 2 X 2 ANCOVA (ADHD X Session, age was covaried) has been performed on the standard deviations of RTs of correct responses, in order to investigate the variability of each subject during the task. A further analysis was carried out to study the effect of each error on the subsequent trial, which relates to the ability to self-regulate the response speed. Thus, an ANCOVA (ADHD was the main factor, age covaried) was carried out on the differences between RTs after each commission

error and RTs of the correct responses. A log transformation was applied in order to normalize the skewness of the distribution.

Correct response RTs. The results are reported in figure 8.1. Sessions (1 and 2) are constituted of 180 stimuli and each Session is composed of two Blocks (A and B).

Figure 8.1.

SART: RTs of correct responses. Study 1.



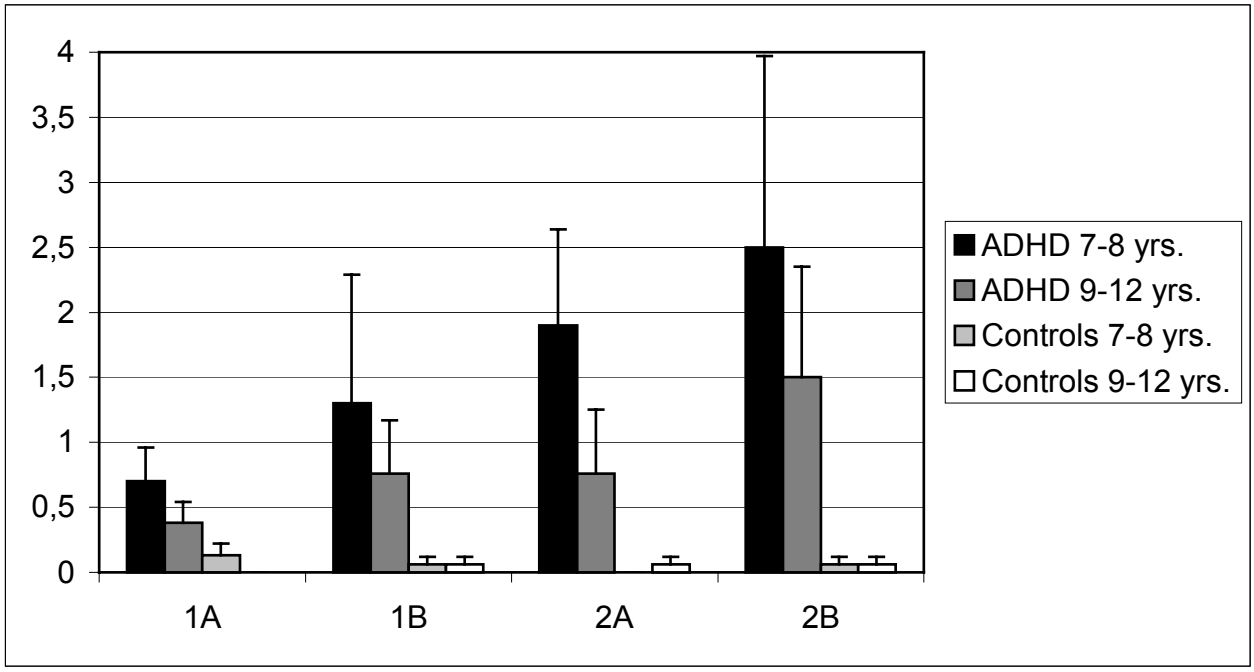
Note: Sessions (1 and 2) are constituted of 180 stimuli. Each Session is composed of two Blocks (A and B). Between the two Sessions there was a break of 60 seconds. Semi-bars represent standard error.

The effects of ADHD [$F(1,59) = 8.543$, $p < .01$, $Eta^2 = .126$] and of age [$F(1,59) = 11.178$, $p < .01$, $Eta^2 = .159$] were significant. As far as the performance over the task is concerned, the Session and the Block effects were not significant. The interactions Session by ADHD or Block by ADHD were not significant, but the interaction Block by age was significant [$F(1,59) = 6.985$, $p < .05$, $Eta^2 = .106$], because the performance of the younger children decreased more rapidly than the performance of the older children.

Omission Errors. The results are reported in figure 8.2.

Figure 8.2.

SART: Omission Errors. Study 1.



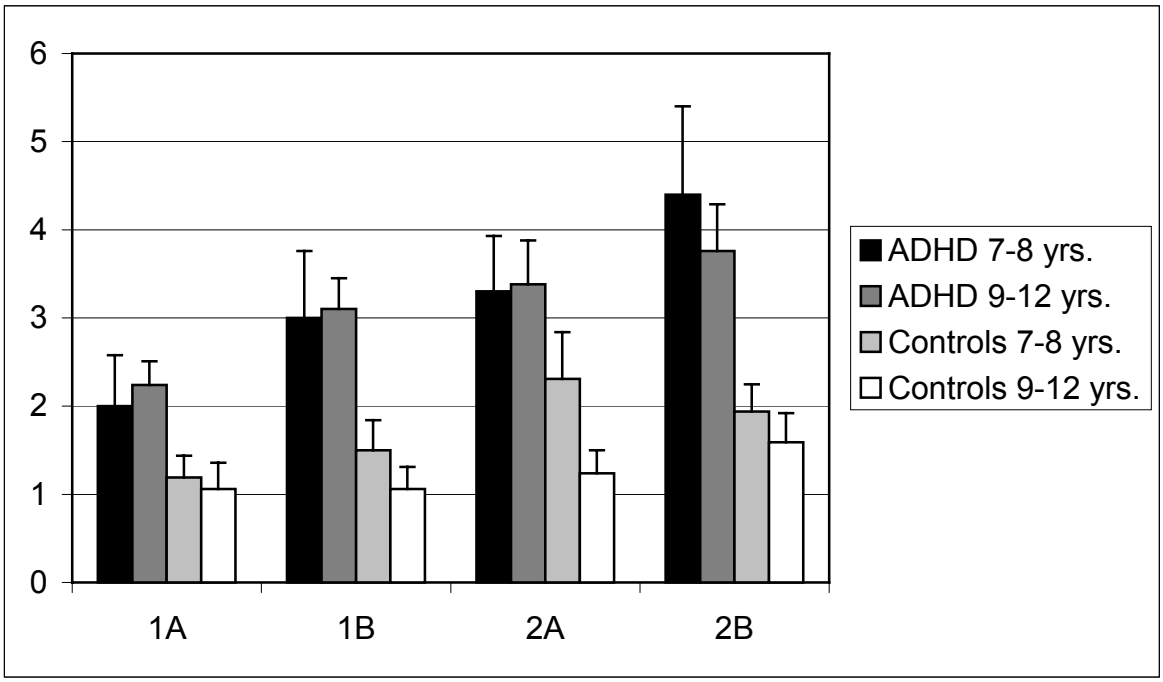
Note: Sessions (1 and 2) are constituted of 180 stimuli. Each Session is composed of two Blocks (A and B). Between the two Sessions there was a break of 60 seconds. Semi-bars represent standard error.

There was a significant effect of ADHD [$F(1,59) = 16.072$, $p <. 001$, $Eta^2 = .211$] for Omission Errors. The Session and Block effects were not significant, but the interaction ADHD by Session was significant [$F(1,59) = 5.098$, $p <. 05$, $Eta^2 = .078$], because children with ADHD performed more poorly than Controls, more in Session 2 than in Session 1.

Commission Errors. The results are reported in figure 8.3.

Figure 8.3.

SART: Commission Errors. Study 1.



Note: Sessions (1 and 2) are constituted of 180 stimuli. Each Session is composed of two Blocks (A and B). Between the two Sessions there was a break of 60 seconds. Semi-bars represent standard error.

There was a highly significant effect of ADHD on number of Commission Errors [$F(1,60) = 30.381$, $p < .001$, $Eta^2 = .332$]. Neither Session nor Block effects were significant.

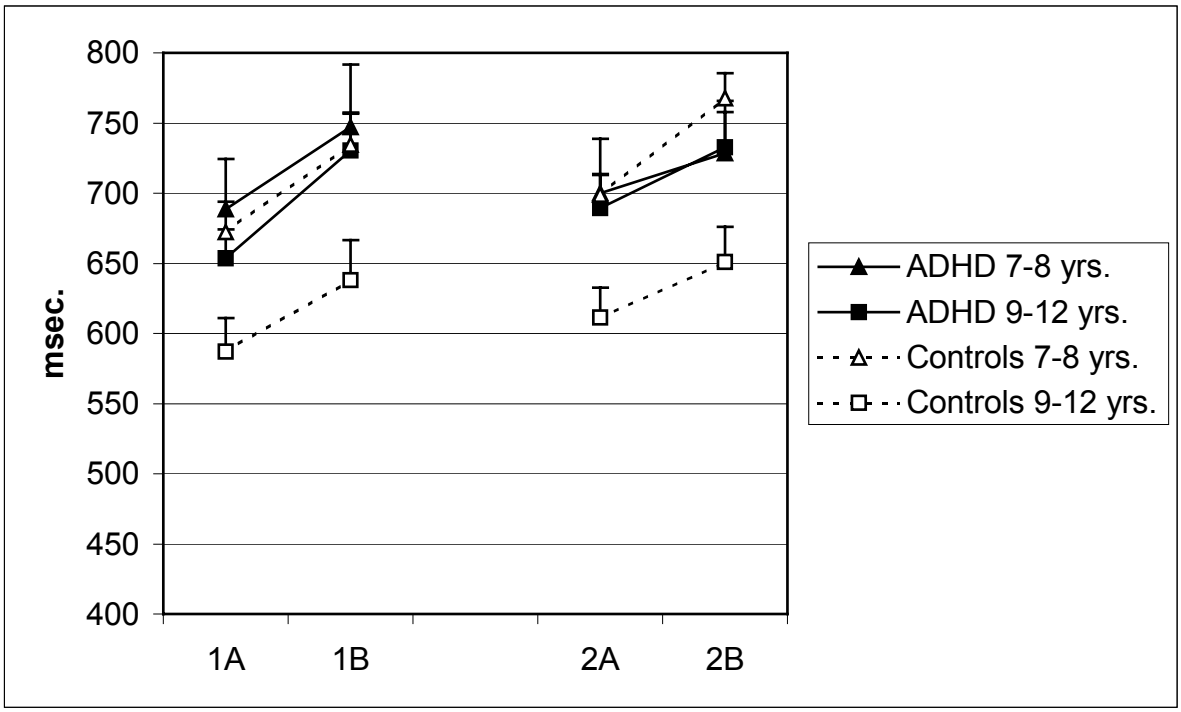
RTs after a commission error. A comparison was carried out between ADHD and Controls on the difference between median RTs in the trial immediately after a commission error and the median RTs of correct responses. On this parameter the children with ADHD slowed down significantly less than Controls (ADHD 39 msec.; NC 105 msec.) [$t(40) = 2.37$, $p < .05$].

b. Vigilance task

Two 2 X 2 X 2 ANCOVAs (ADHD X Session X Block, age was covaried) were carried out on RTs of correct response and on number of Omission Errors. The results for RTs of correct responses are reported in figure 8.4.

Figure 8.4.

Vigilance task: RTs of correct responses. Study 1.



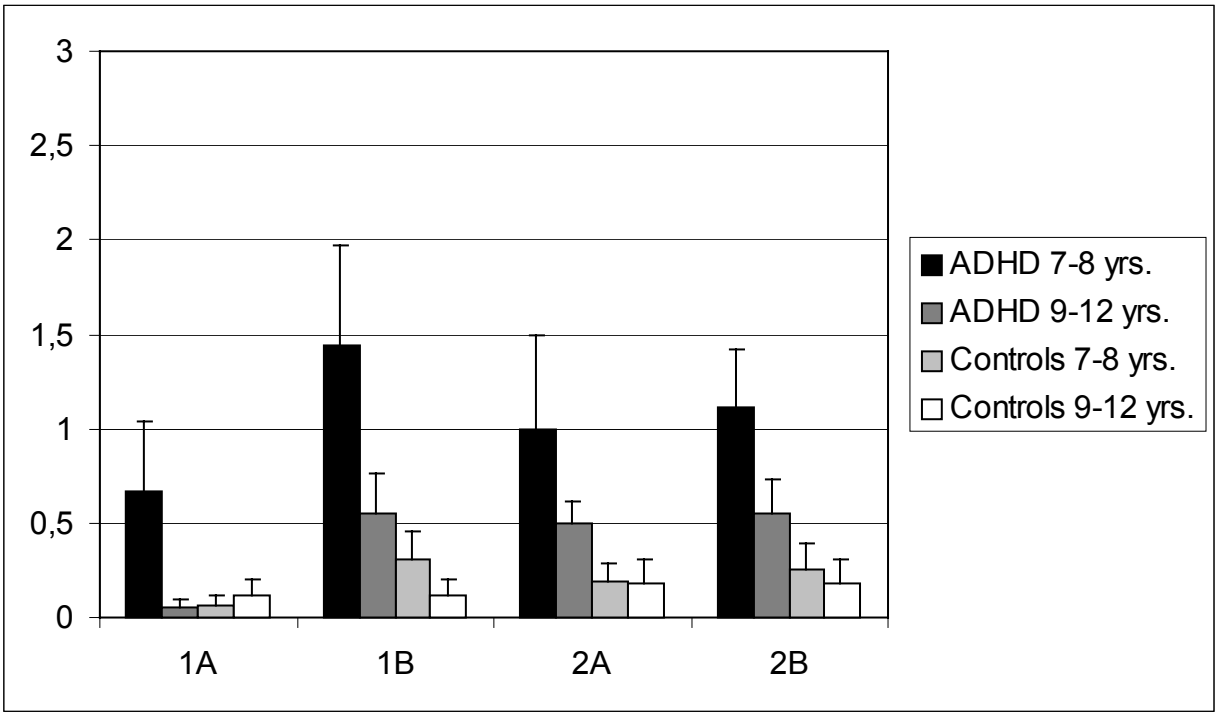
Note: Sessions (1 and 2) are constituted of 180 stimuli. Each Session is composed of two Blocks (A and B). Between the two Sessions there was a break of 60 seconds. Semi-bars represent standard error.

There were significant effects of ADHD [$F(1,58) = 4.554$, $p < .05$, $Eta^2 = .073$] and of age [$F(1,58) = 6.965$, $p < .02$, $Eta^2 = .107$] for RTs of correct responses. The Session and the Block effects were not significant. The interactions were not significant as well.

The results for Omission Errors are reported in figure 8.5.

Figure 8.5.

Vigilance task: Omission errors. Study 1.



Note: Sessions (1 and 2) are constituted of 180 stimuli. Each Session is composed of two Blocks (A and B). Between the two Sessions there was a break of 60 seconds. Semi-bars represent standard error.

For Omission errors there were two significant effects: ADHD [$F(1,59) = 19.340$, $p<.001$, $Eta^2 = .245$] and age [$F(1,58) = 7.015$, $p<.01$, $Eta^2 = .085$]. The Session and the Block effects were not significant. The other interactions were not significant as well.

c. Number Stroop task

A MANCOVA (ADHD was the main effect, age was covaried) was carried out on response speed and accuracy for both the naming and the counting tasks. The results are reported on table 8.1.

Table 8.1.

Results for the Number Stroop task. Study 1.

Measures	ADHD 7-8 yrs. (n = 10) Mean (SD)	ADHD 9-12 yrs. (n = 21) Mean (SD)	Controls 7-8 yrs. (n = 16) Mean (SD)	Controls 9-12 yrs. (n = 17) Mean (SD)
Naming				
Errors	2.20 (2.10)	2.70 (2.87)	1.19 (1.11)	1.06 (1.09)
RT (msec.)	678 (123)	587 (75)	607 (74)	538 (71)
Counting				
Errors	1.30 (1.16)	3.15 (2.68)	0.69 (1.11)	1.47 (1.50)
RT (msec.)	2113 (534)	1840 (334)	1837 (389)	1565 (332)

Note. Naming = the Ss. must name the numbers presented on the screen. Counting = the Ss. must count how many numbers were presented on the screen.

For accuracy in both naming and counting tasks, only the ADHD effect was significant [$F(1,59) = 7.212$, $p < .01$, $Eta^2 = .107$; $F(1,59) = 7.115$, $p < .01$, $Eta^2 = .106$]. For response speed in naming task, both the effects of ADHD and age were significant [$F(1,59) = 7.992$, $p < .01$, $Eta^2 = .115$]; [$F(1,59) = 12.969$, $p < .001$, $Eta^2 = .173$], respectively. Finally, for response speed in counting task the effects of ADHD and age were again both significant [$F(1,59) = 10.911$, $p < .01$, $Eta^2 = .151$]; [$F(1,59) = 14.951$, $p < .001$, $Eta^2 = .210$], respectively.

d. Modified Silhouette Task

A Oneway ANCOVA (ADHD was the main factor, age covaried) was performed on the number of correct responses on the Modified Silhouette task. The age effect was significant [$F(1,63) = 8.500$, $p < .01$, $Eta^2 = .116$], but the ADHD effect was not [$F(1,63) = 0.582$, n.s.]. The results were the following: ADHD = 12.81 (2.64); Normal Controls = 12.09 (1.94).

8.2.4 Discussion

In study 1 the attention performance of children with ADHD have been compared with performance of Normal Controls. The Alerting system was measured considering the response speed and the omission errors in the SART and in the Vigilance task because they reflect the ability to maintain an appropriate level of arousal that enhances to respond rapidly to all targets. The effects of ADHD and of age were both significant, although the magnitude of the effects were higher in the SART, perhaps because the SART was more demanding than the Vigilance task in term of attentional requests: in the SART subjects had to name all the digits but one target out of nine stimuli; in the Vigilance task children had to name only one digit out of nine. As far as the RTs of correct responses is concerned, the interaction ADHD by age was not significant, leading us to hypothesize that children with ADHD follow a normal, though delayed, trend of development. In fact the response speed of the older ADHD children overlapped the response speed of the younger controls (it seems that ADHD children presented a delay of about a couple of years in terms of readiness to respond). Instead, as far as the number of omissions of the SART is concerned children with ADHD performed significantly more poorly than normal controls, and the developmental lag effect was not observed. Therefore it is possible that ADHD is not a generalized developmental lag condition and that these children suffer only from a maturational delay, which could recover during adolescence when cognitive development reaches its conclusion, because the performance shown by children with ADHD on omission errors of the SART did not follow the same trend of the RTs of correct responses.

Another interesting result derives from the observation that children with ADHD did not consistently present with decrement of performance across blocks within a session particularly with respect to response speed on both SART and Vigilance task. This result is a confirmation that ADHD is not characterized by a specific and linear decrease of attentional resources. Moreover, the variability of the response speed (standard deviation of RTs) revealed that the performance of

children with ADHD was particularly inconsistent, confirming that one of the major problem of ADHD is the inability to control attentional lapses. Robertson et al (1997) proposed that the main problem of patients with frontal / executive disorders (mainly with lesions in the Right Prefrontal lobe) is the difficulty to control lapses of attention that induce to inhibitory and action control deficits. This explanation could fit with the notion that children with ADHD could be characterized by a Right Prefrontal dysfunction that impair their attentional control skills.

The Executive Control system has been measured using three variables: Commission errors of the SART, Errors and RTs in the Counting task of the Number Stroop. Children with ADHD made more Commission errors than normal controls. Moreover, they increased the number of errors in the second block of each session: this means that their attentional difficulties affected more the ability to avoid errors rather than worsening their readiness to respond. Interestingly, on the number of Commission errors the age effect was not significant: both ADHD and Controls did not show significant differences in the two age ranges. It could be possible that the inhibitory skills reach their full development, in the control group, before the age of 7 (Hughes, 2002). Instead, the inhibitory skills are hardly acquired by ADHD children even when they are pre-adolescents (for a review, Barkley, 1997; Quay, 1998). Moreover, the Executive control system was assessed considering Errors and RTs of the Counting task of the Number Stroop. For both variables the effect of both ADHD and of age were significant: like for the response speed of the SART and Vigilance task, the group of older ADHD performed like the younger controls: the developmental lag hypothesis for the readiness to respond is confirmed by the results on the Number Stroop. A second interesting result on the Errors of the Number Stroop is the age effect: the older children of both groups made more errors than the younger children. This result could be due to the developing automaticity of number recognition and naming: for this reason the older children were faster in naming than counting digits and they were more affected by the Stroop effect, so they produced more errors. As far as the Errors in the counting task of the Number Stroop is concerned, the difference between ADHD and controls increased over the ages and it could be interesting to

compare adolescents ADHD and Controls on this measure, in order to study if the inhibitory skills develop also in ADHD during adolescence and help them to control the conflicting responses.

Finally on the Modified Silhouette Task ADHD children were not impaired although an age effect was present. In other words, the right infero-temporal functioning is still developing in the age window from 7 to 12 years, but children with ADHD do not suffer of any deficit of this type.

From this set of results, following the Posner and Peter's (1990) model of attention, we can argue that children with ADHD have some impairments in the Alerting and Executive Control systems, but not on the Orienting system. From a neuro-anatomy point of view, it is plausible that ADHD is characterized by a dysfunction in the Right Prefrontal lobe, in the Anterior Cingulate gyrus and in some other sub-cortical regions, such as Globus Pallidus and Nuclei Caudate. The proposal of this neurological network for ADHD has been already demonstrated using neuroimaging techniques (Castellanos et al., 1996).

8.3 Study 2

8.3.1 Aims of study 2

In study 2 several modifications to the experiments were realized in order to test specific hypothesis: 1) the presentation rate of the stimulus (ISI) of the SART was different between the two sessions (the ISI of the fast condition was 1.5 sec and the ISI of the slow condition was 2.5 sec). The creation of two sessions with different rate of presentation of the stimuli was for testing the hypothesis (according to Sergeant et al., 1999) that children with ADHD mostly suffer of a defective system for the state regulation: in order words the ADHD children are not able to sustained their own attention when the presentation rate of the stimuli are particularly slow, but behave normally when the speed of the stimuli is fast. On the hand the children with RD may present a speeded processing and their impairments become particularly visible when the presentation rate of the stimuli is fast. According to Sergeant's et al (1999) theory we expected that

children with ADHD were impaired in the slow condition and those with RD were impaired in the fast condition.

The Vigilance task was created using two different rate of presentation of the stimulus, as the SART; moreover the comparison between the performance on the SART and the Vigilance task is necessary to test whether children with ADHD are more impaired (slower responses) when the task demands inhibitory processes (such as SART) or when the task is not energetically activating (such as the Vigilance task).

Finally the Number Stroop task was modified with the inclusion of a baseline condition (counting neutral stimuli) in order to obtain more reliable data on RTs of non-automatic responses. The hypothesis is that the difference of RTs in counting conflicting stimuli (numerals) and RTs in counting neutral stimuli (stars) is higher in children with ADHD because they may present more severe impairment in controlling conflicting responses due to their Executive dysfunctions.

8.3.2 Material

a. Sustained Attention Response Task (SART)

The children were presented with numerals, one at time, in two 7-minute sessions, with a pause of 1 minute between them. Digits were presented on a laptop screen (14") at 0.70 cm. distance. The SART had two conditions according to the presentation rate of the stimuli: Slow and Fast. The Slow condition had an inter-stimulus interval (ISI) of 2500 msec. and the stimulus disappeared when the child named the numeral (112 in total), or after 2 seconds. The children were asked to name all the numerals presented on the screen except for the target (number "3"). The Fast condition had an ISI of 1500 msec. and the stimulus disappeared when the child named the numeral (180 in total), or after 2 seconds. The children were required to name all the numerals presented on the screen except for the target (number "7"). The order of sessions was counterbalanced. The number of stimulus for the two conditions (Slow and Fast) were different in order to match the time length of the tasks. RTs of correct responses were recorded, as well as the number of Omission

errors (when a non-target numeral was not named), and the number of Commission errors (when a target numeral was named).

b. Vigilance Task

The stimuli and procedure were similar as in the SART except for the task: participants were asked to name only the target (in the slow condition the target was "2" and in the fast condition it was "6"). In the slow condition the numerals presented were 81, and in the fast condition the numerals were 113, the different number of stimulus was due to the need to match the time length of the two conditions. Moreover, compared to study 1, the SART and the Vigilance task of study 2 give the children the possibility to respond also after 1000 msec., therefore it is expected that, in general, their RTs are slower than in study 1.

c. Number Stroop task

In this test children were required to name or to count numbers or stars. Compared to study 1, the trials were divided into three sessions each having 48 sets of stimuli. The sets were composed from two to seven identical stimuli (stars or numerals). In the first session, the task was to count (sub-vocally) the stars presented on the screen. This session (counting stars) was introduced in order to obtain the baseline MRT for counting from two to seven stimuli. In the second session, the task was to name the numerals presented on the screen (just once, as they were all the same). This session was run in order to have a MRT of naming digits and to train the children to name numerals. In the third session, the task was to count the number of digits. The number of errors (the child named the digits instead of counting them, due to the "Stroop effect") and the RTs of the correct responses were recorded. The difference of RTs between counting and naming numerals was computed in order to obtain a parameter that describes the cost of inhibiting an automatic response (naming numerals) and of activating a controlled response (counting numerals).

d. Rotated Blackboard test

The children were presented with twelve cards each containing two pictures of blackboard in the same card. Both blackboards were depicted in order to underline their orientation with the inclusion of spatial markers (legs and supports of the blackboard). The upper blackboard contained ten common pictures (phone, airplane, hand, and so on) and the bottom blackboard was rotated (four trials in the upright position, four trials rotated of 90° on the right, four trials rotated of 90° on the left, and four trials upside-down). The bottom blackboard contained a window which surrounded exactly one of the ten objects, according to the degree of the rotation. The subjects must point a picture (on the upper blackboard) which could be surrounded by the window of the bottom blackboard. The number and the RTs of correct responses had been recorded.

e. Object naming task

The subjects were presented with a card containing fifty pictures of common objects partly overlapped. The task was to name as fast as possible the objects. The number of errors and the speed of responses were recorded.

8.3.3 Statistical analysis

As described in chapter 7, in the second study we were interested both to replicate the results obtained in study 1 and to analyse more deeply the effect of the presence of ADHD and / or RD on Attention tests. For this reason, each task was analysed running two sets of statistics:

1) an ANCOVA, with ADHD as main factor and the age as covaried, in order to detect any specific effect due to the presence of ADHD, but keeping into account also a developmental issue. Related to this analysis we reported the performance of ADHD and the control children only (excluding the RD condition), splitting the two groups in two further subgroups according to the age (as we did in study 1: ADHD 7–8 years (N = 26), ADHD 9-12 years (N = 29), NC 7-8 years (N = 9), NC 9-12 years (N = 28).

2) A 2 x 2 ANCOVA (ADHD and RD were the two main effects, age was covaried). This analysis was run in order to detect the effect on the performance due the presence of ADHD, RD and the interaction. When an interaction ADHD by RD was present, two further analysis had been carried out in order to find out differences among the clinical groups (an ANCOVA) or between each clinical group and normal controls.

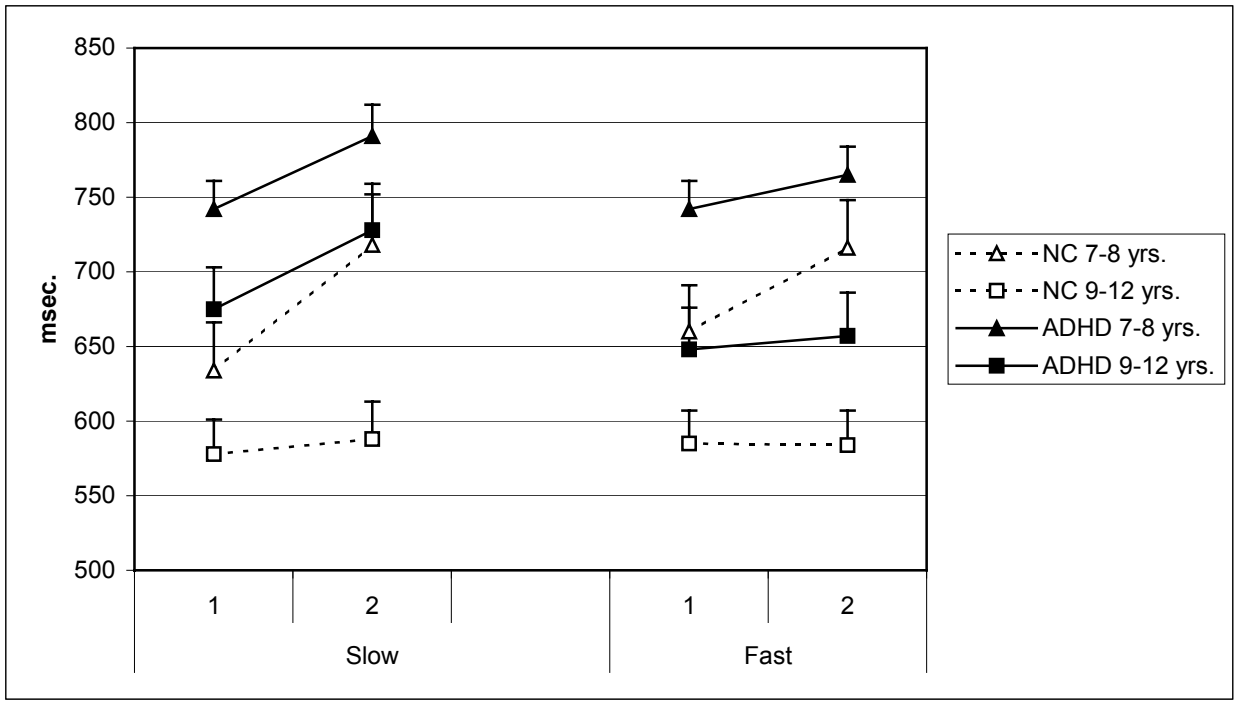
8.3.4 Results

a. Sustained Attention Response Task (SART)

Correct response RTs. A log transformation was applied on the RTs in order to reduce the skewness and to normalize the distribution. The results are reported in figure 8.7.

Figure 8.7.

SART: RTs of correct responses (RD not included). Study 2.



Note. Semi-bars represent Standard Errors.

Considering only the controls and the group with ADHD, a 2 x 2 x 2 ANCOVA (ADHD x Rate x Block, age was covaried) was performed on the RTs of the correct responses. The age effect was significant, because the older children were significantly faster than the younger ones: [$F(1,80) = 25.721$, $p < .001$, $Eta^2 = .243$]; the ADHD effect was also significant [$F(1,80) = 16.541$, $p < .001$, $Eta^2 = .171$]. These results replicated the findings obtained in study 1 (ADHD and age effects). The Block effect was significant [$F(1,80) = 10.830$, $p < .01$, $Eta^2 = .119$], due to the faster responses in the first half of each session. The interaction ADHD by Rate was significant [$F(1,80) = 4.268$, $p < .05$, $Eta^2 = .051$]. The interaction ADHD by Block was not significant.

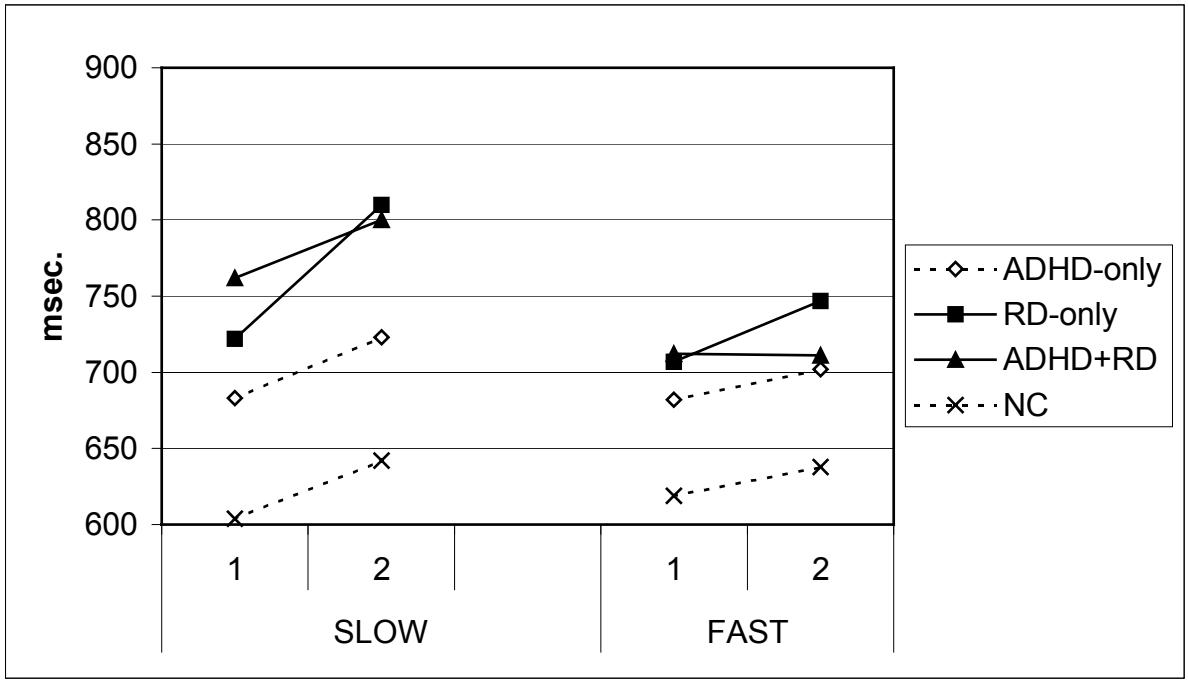
These results are in line with the argument proposed by Sergeant et al. (1999) and Douglas (1999) who claimed that, due to their self-regulatory deficit, children with ADHD are particularly slow when the presentation rate of the stimuli is slow and, that children with ADHD do not present a specific attention deficit because their performance did not decrease linearly across the task.

Comparing the figures 8.1 and 8.7 it is clear that only older control children gave the same results across the two studies, but the group with ADHD and younger controls gave slower responses of about 50-100 msec. compared to ADHD and younger controls of study 1. As mentioned above, this difference is due to the different parameters of the SART of study 2 which gave the possibility to record the responses longer than 1000 msec (in study 1, this was not possible).

Considering all subjects (ADHD-only, RD-only, ADHD+RD and Controls), a 2 x 2 x 2 x 2 ANCOVA (ADHD x RD x Rate x Block, age was covaried) was performed on the RTs of the correct responses of the SART because we were interested to analyze which condition (ADHD or RD) affected more the speed of response.

Figure 8.8.

SART: RTs of correct responses (RD included). Study 2.



Note: Values are corrected by age.

The RD effect was significant [F (1,111) = 16.678, $p < .001$, $Eta^2 = .131$], the ADHD effect approached significance [F (1,111) = 3.181, $p < .08$, $Eta^2 = .028$] and the interaction ADHD by RD was significant as well [F (1,111) = 5.026, $p < .05$, $Eta^2 = .043$]. Since the ADHD by RD interaction

was significant pairwise comparisons were carried out between each clinical group and Controls. All comparisons revealed significant differences: ADHD-only ($p = .001$), RD-only ($p < .001$) and ADHD+RD ($p < .001$); therefore the interaction appeared to be due to the lack of an additive effect.

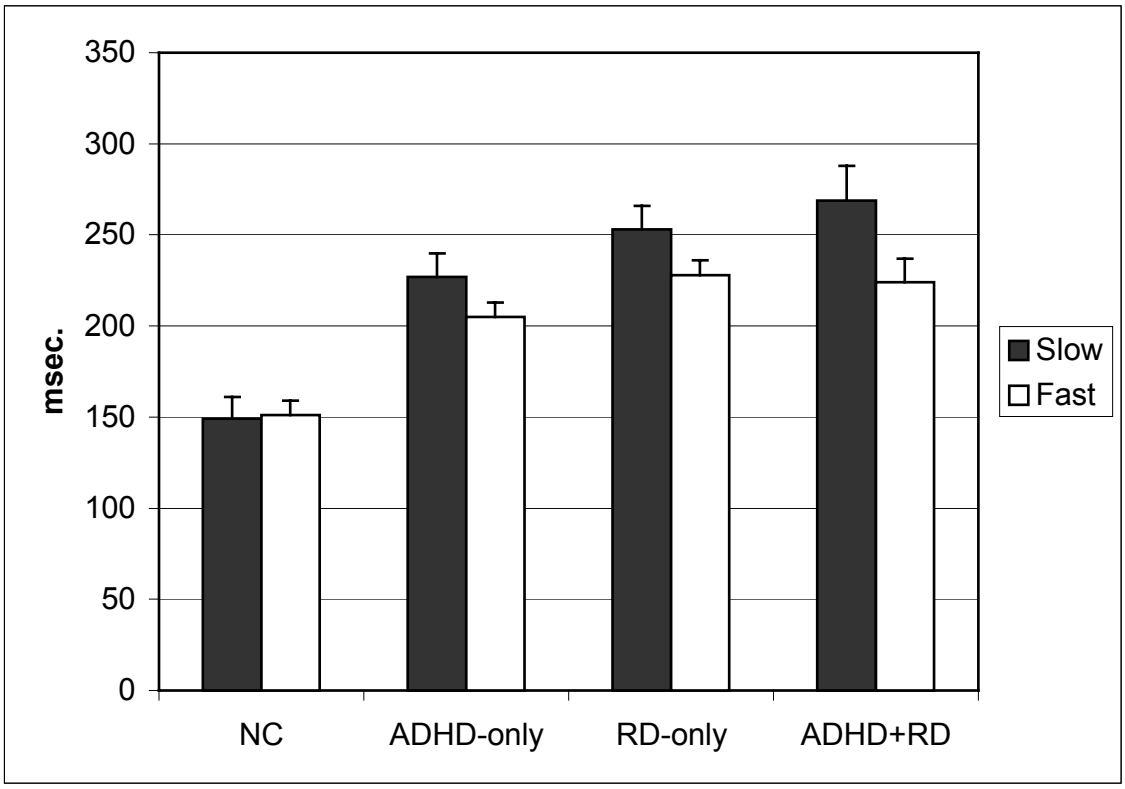
The Rate effect was not significant but the Block effect was significant [$F(1,111) = 15.192$, $p < .001$, $Eta^2 = .120$] because all children slowed down in the second half of each session. The interaction Rate by ADHD was not significant but the interaction Rate by RD was significant [$F(1,111) = 8.328$ $p < .01$, $Eta^2 = .065$]. This result indicated that the presence of RD, not ADHD, caused a decrease in the response speed when the presentation rate of the stimuli was slow. In other words, if only the ADHD condition is considered, the model proposed by Sergeant et al (1999) is confirmed because children with ADHD are slower in the slow presentation rate condition; but if the Reading Disorder diagnosis was included into the analysis, the pattern of results went into the opposite direction: children with RD were slower in the slow condition (not in the fast condition).

Standard Deviation of RTs

In order to analyze the performance consistency of the four groups a 2 x 2 x 2 ANCOVA mixed design (ADHD x RD x Rate, age covaried) was performed on the Standard Deviations of the RTs. The standard deviation of RTs data, corrected by age, are reported in figure 8.9.

Figure 8.9

SART: Standard Deviation of RTs (RD included). Study 2.



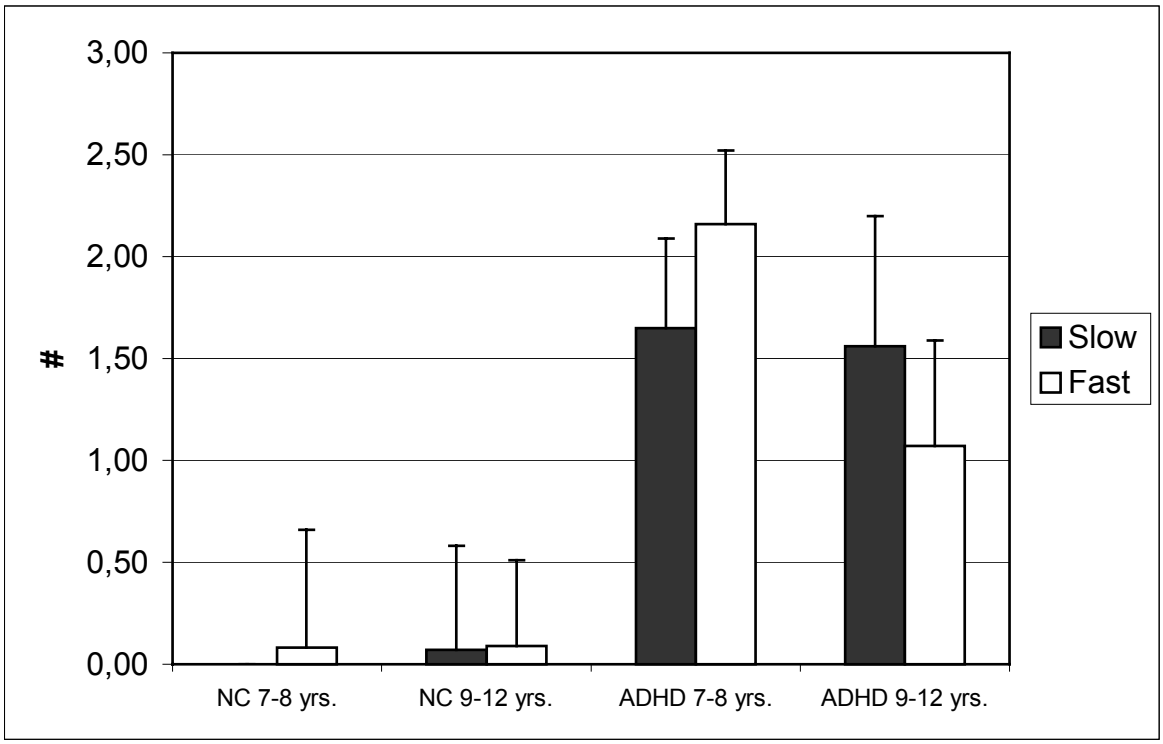
Note: Values are corrected by age. Semi-bars represent Standard Error.

The effects of both ADHD and RD were significant, respectively, [F (1,110) = 14.001, p < .001, Eta^2 = .113] and [F (1,110) = 39.539, p < .001, Eta^2 = .264]; also the interaction ADHD by RD was significant as well, [F (1,110) = 17.197, p < .01, Eta^2 = .135]. Since the ADHD by RD interaction was significant pairwise comparisons were carried out between each clinical group and Controls. All comparisons revealed significant differences (p < .001), therefore the interaction was due to the lack of additive effect of both ADHD and RD conditions on children with ADHD+RD.

Omission errors. Considering only children with ADHD and Controls, a 2 x 2 ANCOVA mixed design (ADHD by Rate, age was covaried) was performed on the number of Omission errors. The results are reported in figure 8.10.

Figure 8.10

SART: Number of Omission errors (RD excluded). Study 2.



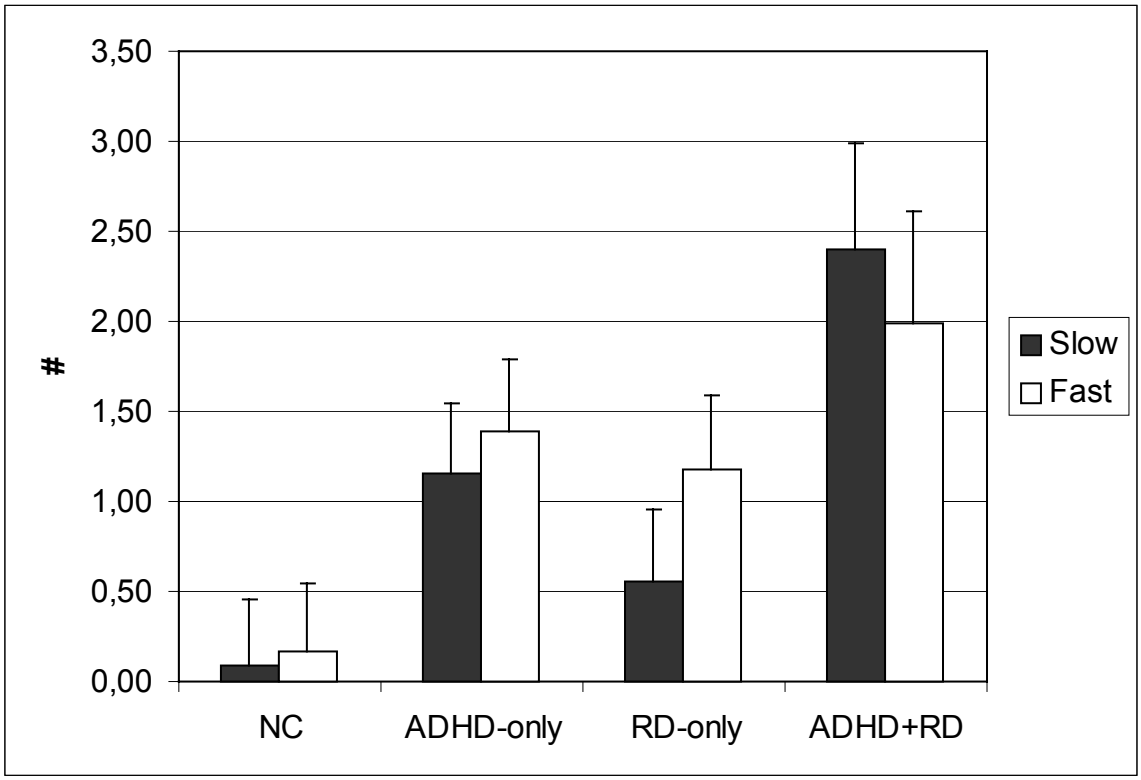
Note. Semi-bars are Standard Errors

The ADHD effect was significant [F (1,78) = 10.331, $p < .01$, $Eta^2 = .117$], but the Rate effect and the interaction Rate by ADHD were not significant. These results replicate exactly what found in study 1.

A second 2 x 2 x 2 mixed ANCOVA (ADHD x RD x Rate, age was covaried) was performed including also children with RD. The results are reported in figure 8.11.

Figure 8.11

Number of Omission errors (RD included). Study 2.



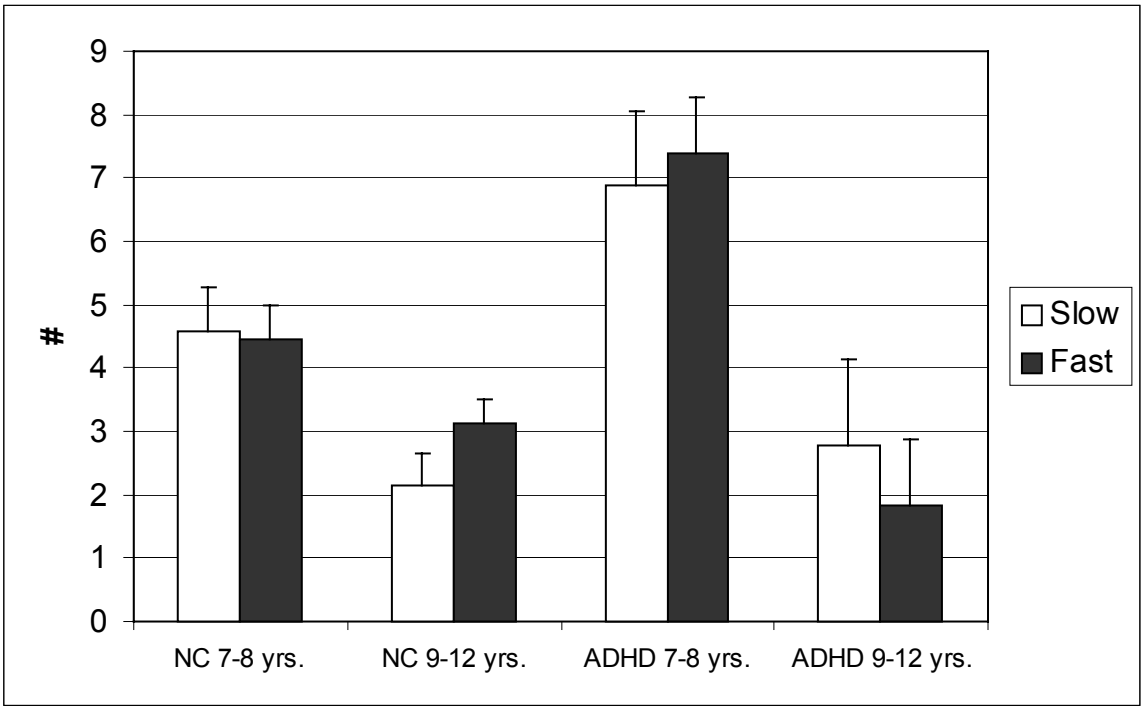
Note. Semi-bars are Standard Errors.

The three main effects were significant: age, ADHD and RD, respectively: [F (1,107) = 4.916, $p < .05$, $Eta^2 = .041$], [F (1,107) = 9.005, $p < .01$, $Eta^2 = .078$], [F (1,107) = 4.333, $p < .05$, $Eta^2 = .039$]. The Rate effect and the interaction were not statistically significant.

Commission Errors. In order to investigate the inhibitory skills of the children with ADHD and / or RD, the number of Commission errors (when the child was not able to suppress the response when the targets "3" or "7" appeared) was analyzed. First of all, a 2 x 2 mixed ANCOVA (ADHD by Rate, age was covaried) was performed on the number of Commission errors including only children with ADHD to replicate study 1. The results are reported in figure 8.12.

Figure 8.12

Commission errors (RD excluded). Study 2.



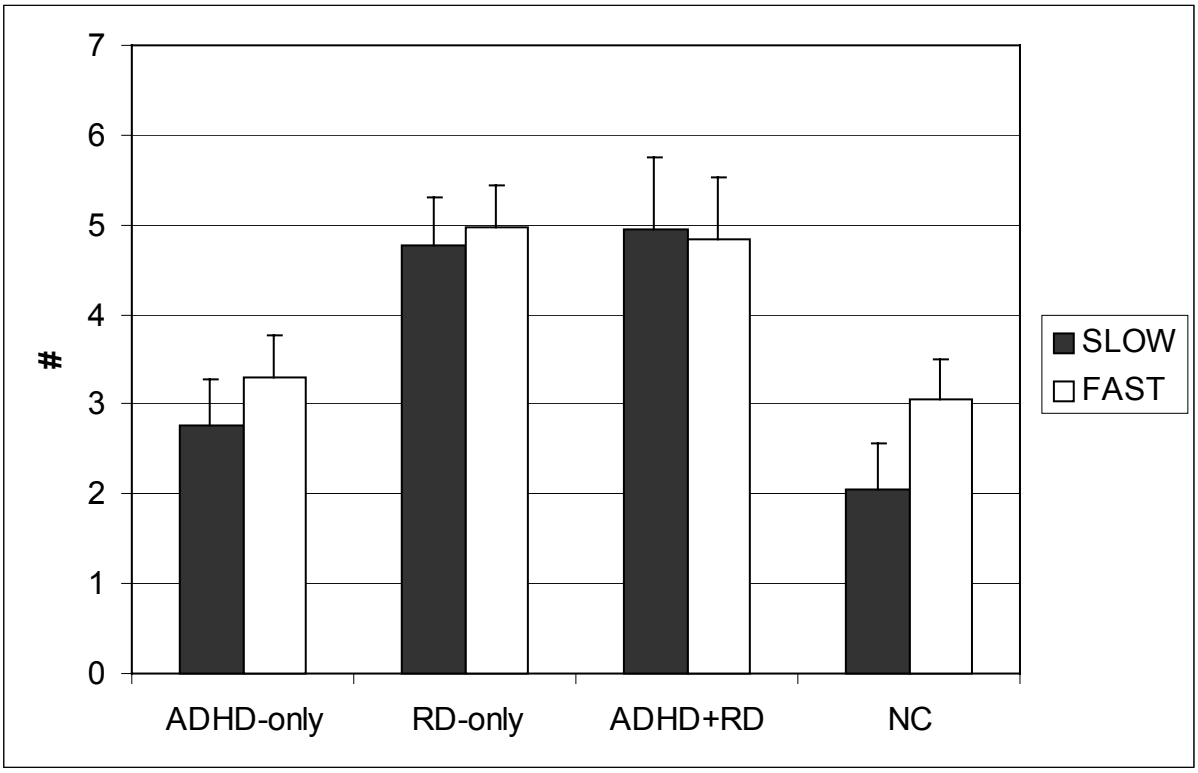
Note. Semi-bars are Standard Errors.

The age and ADHD effects were significant [F (1,78) = 17.296, $p < .001$, $Eta^2 = .226$; F (1,78) = 4.049, $p < .05$, $Eta^2 = .048$, respectively]. The Rate effect and the interactions were not significant. These results partly replicated those obtained in study 1 but the ADHD effect is smaller than in study 1 and the interaction Block by ADHD is now not significant.

Including also the RD condition, a 2 x 2 x 2 ANCOVA (ADHD x RD by Rate, age was covaried) was performed on the number of Commission errors, with the two presentation rate conditions (Slow and Fast). The results on Commission errors produced by children with ADHD-only, RD-only, ADHD+RD and Controls are reported in figure 8.13.

Figure 8.13

SART: Commission Errors (RD included). Study 2.



Note: Values are corrected by age. Semi-bars represent Standard Error.

The age effect was highly significant [F (1,113) = 30.759, $p < .001$, $Eta^2 = .217$] because the younger children made more commission errors than the older children. This effect was not found in study 1. The RD effect was significant [F (1,113) = 21.088, $p < .001$, $Eta^2 = .160$], but the ADHD effect was not significant. The Rate effect and the interactions were not significant, as well.

RTs after a commission error

A Oneway ANCOVA (ADHD as main factor, age was covaried) was performed on the RTs of correct responses after a Commission error considering only the ADHD group for replicating study 1. It was chosen to analyze only the Fast Session because the presentation rate of the stimuli is very similar to study 1. An ANCOVA (ADHD as main factor, age covaried) was performed: the effect of ADHD was not significant: [F(1,69) = 2.224, n.s.]. The results were: ADHD = 158 msec and Controls = 240 msec. However if only the group of children with ADHD-only (excluding those with ADHD+RD) is compared to Controls the effect approached the statistical significance [F(1,57)

= 3.777, $p < .06$, $Eta^2 = .217$]. As in study 1, children with ADHD-only tended to slow down less than Controls (ADHD-only = 132 msec; Controls = 240 msec.). In particular, the difficulty to slow down the responses after a commission error (as a measure of self-regulation) is more specific for the group with ADHD-only than being generalized to all children with ADHD. Moreover, it is necessary to underline that the variability of RTs obtained in study 2 is more precise than that obtained in study 1 because the window of recording is larger (1500 msec) in study 2 than in study 1 (1000 msec).

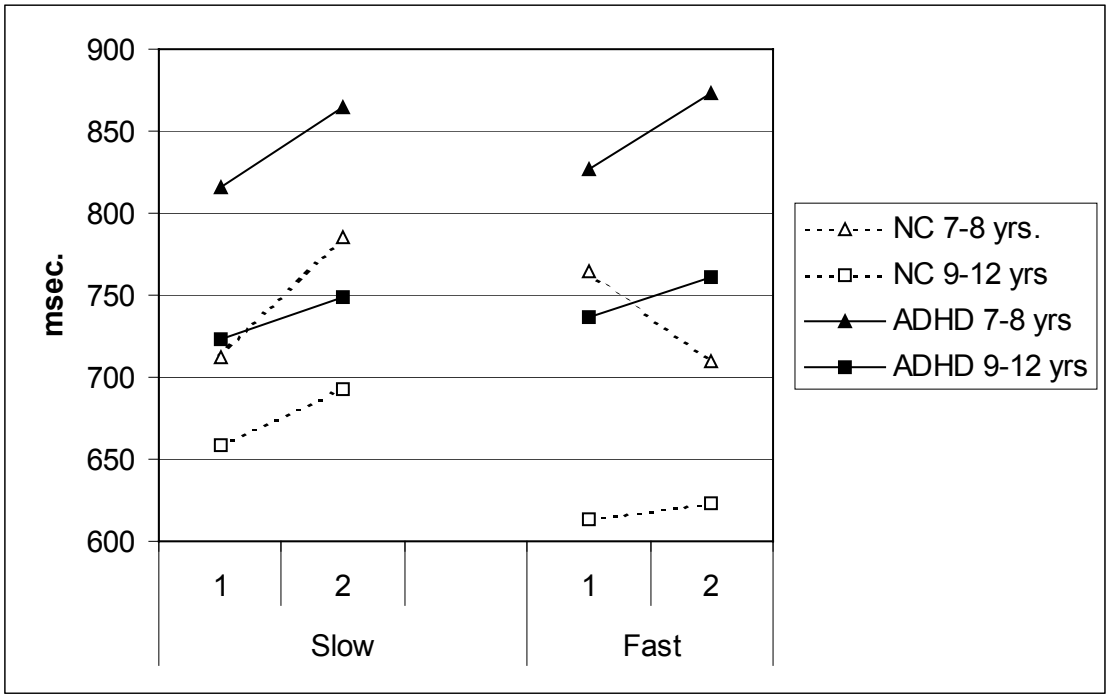
b. Vigilance task

Response Speed

As described above, the stimuli of the Vigilance task were presented at two different Rates (Slow and Fast), moreover, each session was divided in two parts: the first half and the second half (Blocks), in order to detect whether children showed a response speed decrement across the task. A 2 x 2 x 2 ANCOVA mixed design (ADHD by Rate by Block, age was covaried and RD excluded) was performed on the RTs of the correct responses. The RTs data on the Vigilance task are reported in figure 8.15.

Figure 8.15

Vigilance task: RTs of correct responses (RD excluded). Study 2.

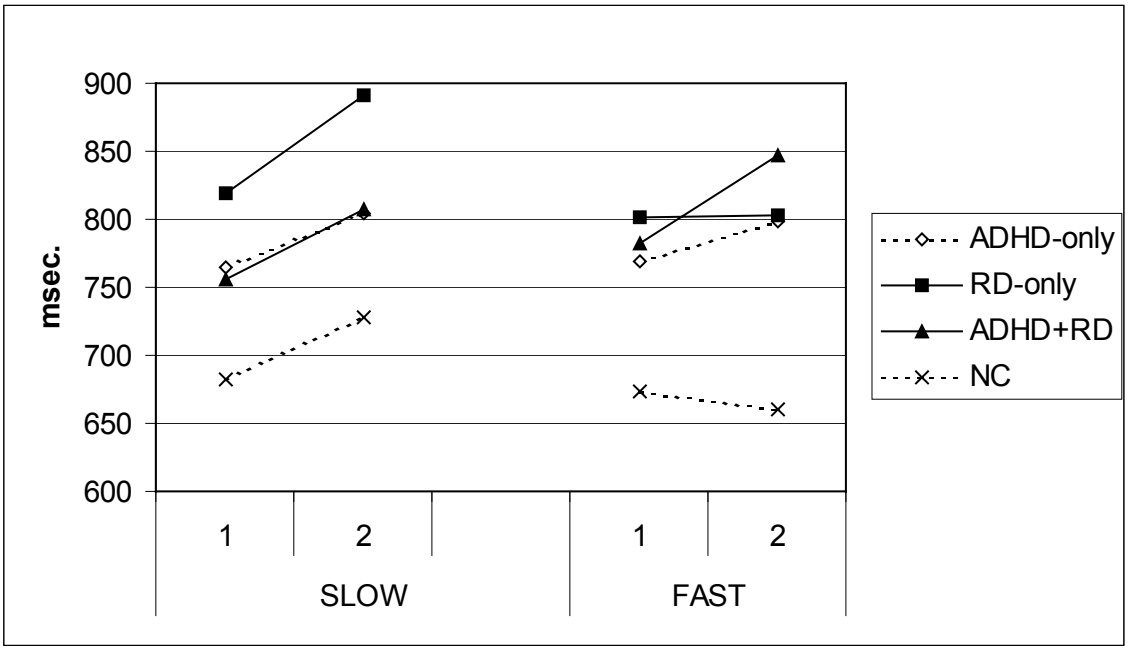


The age effect was significant, because the older children were faster than the younger ones: [F (1,73) = 15.227, $p < .001$, $Eta^2 = .173$]; the ADHD effect was significant as well [F (1,73) = 9.715, $p < .001$, $Eta^2 = .117$]. The Block effect was not significant, but the interaction Rate by ADHD approached significance [F (1,73) = 3.563, $p < .07$, $Eta^2 = .043$].

In order to clarify the role of the two clinical conditions, a second 2 x 2 x 2 x 2 ANCOVA (ADHD x RD x Rate x Block, age was covaried) was performed on the RTs of the Vigilance Task. The results on RTs of the Vigilance task, corrected by age, are reported in figure 8.16.

Figure 8.16

Vigilance task: RTs of correct responses (RD included). Study 2.



Note: Values are corrected by age.

The age effect [F (1,106) = 15.566, $p < .001$, $Eta^2 = .128$] and the RD effect [F (1,106) = 10.310, $p < .01$, $Eta^2 = .089$] were significant. The interaction ADHD by RD was significant as well [F (1,106) = 5.756, $p < .02$, $Eta^2 = .052$]. The interaction ADHD by Rate was significant as well [F (1,106) = 3.988, $p < .05$, $Eta^2 = .036$]. This interaction was due to the longer RTs of Normal Controls and RD children in the slower condition. The same phenomenon (decrease speed of response in the slow condition) was not observed in the two groups of children with ADHD.

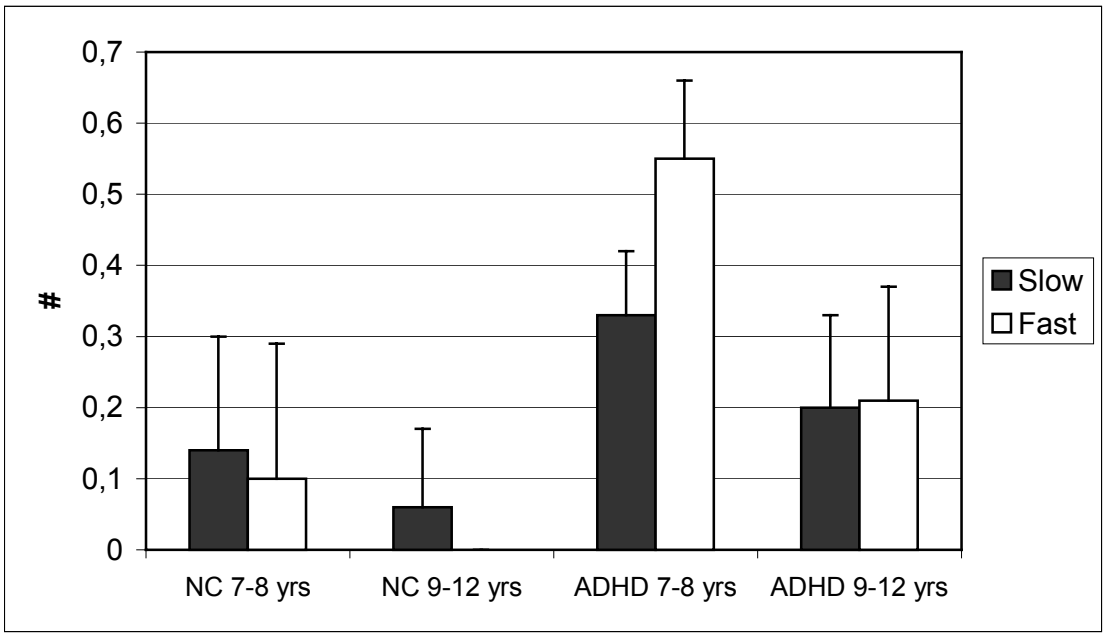
Since the ADHD by RD interaction was significant pairwise comparisons were carried out between each clinical group and Controls. All comparisons revealed significant differences: ADHD-only ($p = .001$), RD-only ($p < .001$) and ADHD+RD ($p < .001$); therefore the interaction appeared to be due to the lack of an additive effect.

Omissions

A 2 x 2 mixed ANCOVA (ADHD by Rate, age was covaried) was performed on the number of Omission errors. The results, considering the two age groups, are reported in figure 8.18.

Figure 8.18

Vigilance task: Omissions (RD excluded). Study 2.



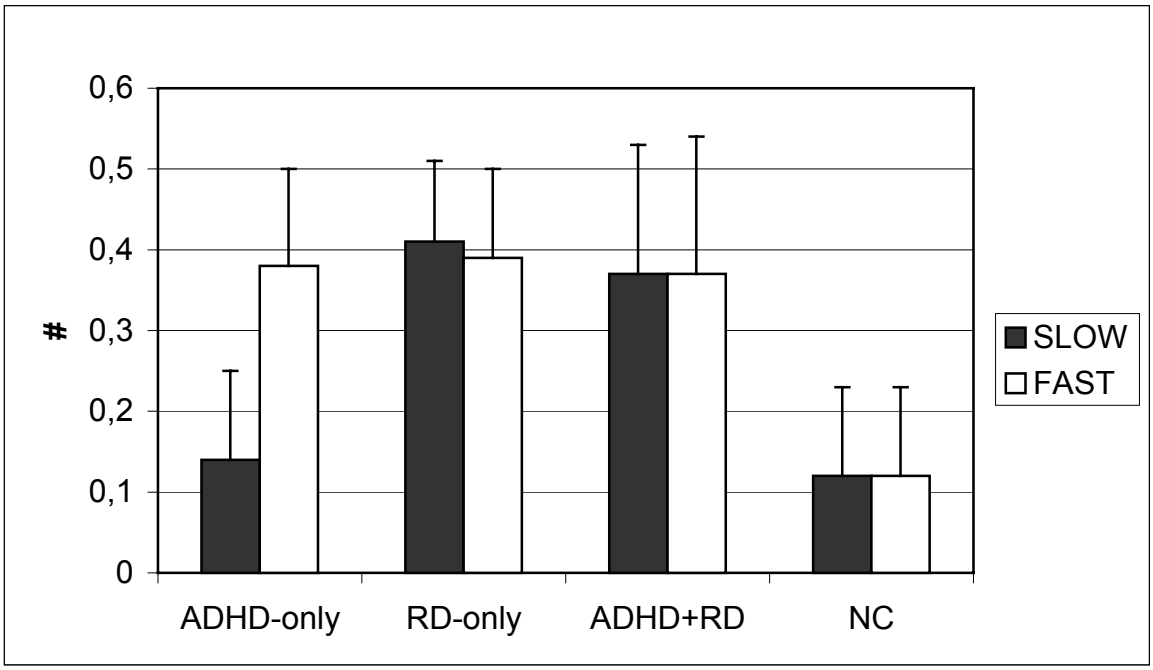
Note. Semi-bars represent Standard Errors.

The age effect [F (1,76) = 5.233, $p < .05$, $Eta^2 = .064$] and the ADHD effect [F (1,76) = 4.696, $p < .05$, $Eta^2 = .033$] were significant. The Rate effect and the interactions were not significant.

A second 2 x 2 x 2 ANCOVA mixed design (ADHD by RD by Rate, age was covaried) was carried out on the number of Omission errors. The results of the four groups, corrected by age, are reported in figure 8.19.

Figure 8.19

Vigilance task: Omissions. RD included. Study 2.



Note: Values are corrected by age. Semi-bars represent Standard Error.

The age effect was significant [F (1,110) = 8.750, $p < .01$, $Eta^2 = .074$] due to the significantly better performance of the older children. The RD effect was significant [F (1,110) = 5.093, $p < .05$, $Eta^2 = .044$], but the ADHD effect and the interaction ADHD by RD were not significant. The Rate effect and the possible interactions were not significant as well.

Finally, concerning the Omission errors to the SART and to the Vigilance Task a 2 x 2 x 2 ANCOVA (ADHD by RD by Task) performed on the number of Omission errors: the ADHD effect was significant: ADHD [$F(1,102) = 6.409$, $p < .02$; $Eta^2 = .059$], and the interaction ADHD by Task [$F(1,102) = 5.437$, $p < .05$; $Eta^2 = .051$]. The interaction was due to the higher number of omission errors produced by children with ADHD (ADHD-only and ADHD+RD) in the SART compared to the omission errors in the Vigilance task.

c. Number Stroop Task

For three sessions of the task (Counting Stars, Naming Digits and Counting Digits) a MANCOVA (ADHD was the main factor, age was covaried) was performed on the speed of response and the accuracy measures, excluding the children with RD. The results of the Number Stroop tasks, splitting the ADHD and the Normal Controls in two age sub-groups are reported in the table 8.2. On table 8.2 the effects due to the Stroop effect are reported: in particular we have reported the number of errors (when a subject named the digit instead of counting them) and the difference of RTs between the baseline (counting stars) and the experimental condition (counting digits).

Table 8.2

Results of the Number Stroop Task (RD excluded). Study 2.

Variables	ADHD 7- 8 yrs.		ADHD 9–12 yrs.		NC 7- 8 yrs.		NC 9-12 yrs.	
	Mean	*(S.D.)*	*Mean*	*(S.D.)*	*Mean*	*(S.D.)*	*Mean*	*(S.D.)*
Counting Stars								
Errors	2.25	(2.68)	1.53	(1.88)	2.10	(3.18)	1.14	(1.11)
MRT	2091	(527)	1596	(249	1982	(529)	1514	(309)
Naming Digits								
Errors	0.14	(0.49)	0	0	0	0	0	0
MRT	744	(294)	599	(94)	634	(101)	562	(112)
Counting Digits								
Errors	2.17	(1.90)	1.33	(1.84)	2.10	(4.31)	0.52	(0.75)
MRT	2321	(531)	1817	(391)	2227	(531)	1510	(321)
Stroop Effect								
Errors	3.92	(2.73)	1.80	(1.57)	2.60	(1.78)	1.38	(1.16)
MRT	230	(518)	220	(371)	244	(219)	- 5	(294)

The age effect was significant for the RTs in all conditions: Counting Stars [$F(1,81) = 39.691$, $p < .001$, $Eta^2 = .358$], Naming Digits [$F(1,81) = 8.716$, $p < .01$, $Eta^2 = .044$], and Counting Digits [$F(1,81) = 59.077$, $p < .001$, $Eta^2 = .400$]. The ADHD effect was not significant. Considering only the older children, the difference between the ADHD and the Normal Controls were significant for the MRT of the Stroop effect [$t(34) = 2.026$, $p < .05$].

A second 2 x 2 MANCOVA (ADHD by RD, age covaried) was carried out on the same variables described above in order to disentangle the RD effect from the ADHD effect. All results of the Number Stroop task are reported on table 8.3.

Table 8.3.

Results of the Number Stroop task (RD included). Study 2.

Variables	ADHD-only		RD-only		ADHD+RD		NC	
	Mean	*(S.D.)*	*Mean*	*(S.D.)*	*Mean*	*(S.D.)*	*Mean*	*(S.D.)*
Counting Stars								
Errors	1.67	(2.61)	2.33	(2.81)	2.80	(2.69)	1.50	(2.77)
MRT	1801	(425)	2105	(440)	1864	(438)	1750	(451
Naming Digits								
Errors	0.07	(0.30)	0.04	(0.29)	0.15	(0.29)	0.03	(0.31)
MRT	673	(196)	672	(202)	688	(202)	602	(208)
Counting Digits								
Errors	1.63	(2.47)	2.27	(2.56)	2.08	(2.55)	1.15	(2.63)
MRT	2025	(468)	2102	(483)	2049	(482)	1834	(497)
Stroop Effect								
Errors	2.53	(2.06)	3.27	(2.13)	4.07	(2.21)	2.02	(2.19)
MRT	224	(484)	-3	(412)	185	(469)	84	(293)

Note: Values are corrected by age.

The effect of ADHD was not significant for any of the variables, although there was a trend of significance for the errors in the Naming Digits condition [$F(1,116) = 3.330$, $p < .07$, $Eta^2 = .029$] and for the Stroop RT effect [$F(1,116) = 3.302$, $p < .07$, $Eta^2 = .029$]. The RD effect was significant for the errors due to the Stroop effect [$F(1,116) = 11.928$, $p < .001$, $Eta^2 = .097$] and for the RTs in the Counting Stars condition [$F(1,116) = 5.707$, $p < .02$, $Eta^2 = .173$]. The interaction ADHD by RD was not significant.

d. Rotated Blackboard and Rapid Object Naming Tasks

Two 2 x 2 ANCOVAs (ADHD by RD, age covaried) were carried out on the Response Speed and accuracy on the Rapid Object Naming and the Rotated Blackboard task. The Rapid Object Naming and Rotated Blackboard tasks results are presented in table 8.4.

Table 8.4

Rapid Object Naming and Rotated Blackboard. Study 2.

Variables	ADHD-only		RD-only		ADHD+RD		NC	
	Mean	*(S.D.)*	*Mean*	*(S.D.)*	*Mean*	*(S.D.)*	*Mean*	*(S.D.)*
Rapid Object Naming								
Errors	4.736	(3.15)	4.322	(1.99)	4.613	(2.62)	4.98	(2.82)
Speed (sec)	86.86	(23.13)	99.34	(26.58)	113.06	(39.28)	80.69	(24.08)
Rotated Blackboard								
Errors	10.13	(1.24)	10.18	(1.44)	10.71	(1.30)	10.01	(1.82)
Speed (sec)	4.38	(2.12)	5.29	(2.40)	5.03	(1.24)	4.52	(2.44)

The RD effect was significant only for the response speed of the Rapid Object Naming task [$F(1,102) = 13.517$, $p < .001$, $Eta^2 = .132$]. The ADHD effect was not significant for any variable.

However children with ADHD+RD were significantly slower than children with ADHD-only [$F(1,34) = 11.007$, $p < .01$, $Eta^2 = .262$].

These results confirmed that children with ADHD did not present any impairment at the Orienting System as showed in study 1. Finally, as predicted by Tannock et al. (2000) ADHD+RD children have a deficit in object naming tasks.

8.3.5 Discussion of study 2 as replication of study 1

SART. As regards the RTs of correct responses of SART the effects of age and ADHD have been replicated in study 2, although the RTs of study 2 were longer by about 50 msec, because in study 1 stimuli were presented for a maximum time of 1000 milliseconds whereas in study 2 the stimulus remained on the screen for 1500 milliseconds in order to record also the slower responses.

As far as the Omission errors are concerned the ADHD effect has been replicated in study 2, the results were very similar. Concerning the Commission errors, in both studies the ADHD effect was significant, although in study 1 the magnitude was higher than in study 2, because in study 2 the normal controls produced more Commission errors (study 1: between 1.1 to 1.5, study 2: between 2.1 to 4.5) and also ADHD children made more commission errors in study 2 than in study 1 (study 1: between 3.3 to 4.3, study 2: 1.9 to 7.2). The higher number of Omissions produced by both groups could be due to the same reason of the increased RTs because the apparatus, in study 2, was able to record all responses because the time window was large enough.

The ADHD effect found in study 1 concerning the RTs after a commission error has been partly replicated in study 2, because the difference between controls approached significance if the group with ADHD-only was considered, therefore the inability to self-regulate the speed of response after a commission error could be a specific characteristics of the pure ADHD and not of the disorder in comorbidity.

Vigilance Task. As far as the response speed on the Vigilance task is concerned, the ADHD effect found in study 1 has been replicated in study 2, although the RTs data in study 2 were longer

of about 70 ms for the same reasons due the differences in the two experiments described above (RTs window of 1000 ms in study 1 and of 1500 ms in study 2). As regards the Omission errors, the effect of ADHD found in study 1 has been replicate in study 2 but children produced fewer Omissions in study 2 than in study 1, because in the study 2 we presented 195 stimuli whereas in study 1, 360 stimuli.

Number Stroop task. As regards the Number Stroop task, the ADHD effect on the RTs of the Naming Digits has been replicated and also the raw data are very similar between the two studies. The ADHD effect found regarding the RTs in the Counting Digits condition has not been completely replicated. As in study 2 the difference approached statistical significance with p of < .07. It is possible that the performance of the second group of younger controls is less reliable than the results obtained in study 1, because the size of the second sample was smaller than in study 1.

8.3.6 General discussion of study 2

In study 2 the SART, the Vigilance Task and the Number Stroop task were modified in order to test more precisely the attention processes of children with ADHD and/or RD. In particular, the presentation rate of the stimuli was differentiated in order to test if the Alerting system could be affected by the speed of the stimuli and the externally induced activation. This manipulation was created because according to Sergeant et al. (1999) children with ADHD are affected by a defective regulation of the state of alerting system (not essentially different from the alerting system here studied). Sergeant et al (1999) found that when the presentation rate of the stimuli is slower the children with ADHD are particularly impaired, but when the rate is faster they become almost normal because they are more activated by the environment. An alternative proposal can be derived from the approach of Stuss et al (2005) who differentiated the Anterior Attention functions in six processes: Energizing, Inhibiting, Adjusting, Monitoring, Control of Logic and Task setting. In particular, according to their proposal, the speed of response to Reaction Time tasks, such as SART and Vigilance task, involved mainly the Energizing processes of Attention.

Given this theoretical framework, on three measures of Energizing Attention (RTs of SART and Vigilance task, and SD of RTs of the SART) a consistent poor performance of children with ADHD was found. Actually, also the RD effect was found to be significant but it is more likely that their impairment could be due to the slow processing of digits (Moore & Andrade, 2001). Moreover, on three measures the performance of children with ADHD+RD was very similar to the performance of children with RD-only, and the additivity effect of ADHD and RD was not found. Moreover the two presentation rates of the stimuli affected the performance of children with ADHD: in the slow condition, ADHD children were slower than in the fast condition, as proposed by Sergeant et al (1999), only if the RD condition was not included into the analysis. Actually if the RD condition is kept into account the effect of the Rate of the stimuli was significant only to the group of RD children. According to this set of results, as for the speed of response, children with ADHD may present a defective regulation of the Energizing process of attention, but the peculiarity of the tasks (rapid naming of digits) produced many significant RD effects that could be due to the slow digit processing of children with Dyslexia. In order to disentangle this question it is necessary to device other experiments in which children must give rapid responses but presenting verbal material (digits, letters or words). Stuss et al (2005) found that adult patients with Superior Medial Frontal lesion were slower than other groups of frontal patients (Inferior Medial, Left or Right Lateral) and Controls. Moreover, Stuss et al (2005) found that patients with Right Lateral Prefrontal lesions were slower than controls and the other groups of patients when the ISI between stimuli was long (6-7 sec). Actually Stuss et al (2005) were not able to disentangle if the side of the lesion (Right Lateral or Superior Medial) was the most crucial variable that could explain the slowing of the responses because patients with Superior Medial lesions are mostly damaged in the Right side. Their results confirm that subjects with Right Prefrontal dysfunction (and not with Left Prefrontal cortex) may be characterized by slow responses on reaction time tasks. Thus, it is possible that children with ADHD may suffer of a deficit in the domain of the Energizing processes of Attention (Alerting system), that could be an expression of their Right Lateral prefrontal dysfunction.

Since the SART has the advantage of producing multiple indexes of the alerting state of the child (more than hundred RTs) the Block effect is informative of the ability to maintain an adequate performance across the task. In both studies, the Block effect for RTs on the SART was significant, that is: all children slowed down after 3-4 minutes of testing, but this effect was not specific for any group. Moreover, ADHD and RD children were more impaired, compared to normal controls, in the first block than in the second block: normal controls worsened relatively much more than the three clinical groups. The problem of the children with ADHD (and also marginally of the children with RD) is that they were not able to control attentional lapses, rather than slowing linearly across the task. This difficulty, of controlling attentional lapses, is possibly due to a deficit in the Alerting system. Robertson et al (1997) hypothesized that patients with frontal damage would show the same problem: namely attention lapses rather than linear decrease of attention. If this is the case the frontal hypothesis for ADHD (perhaps more prevalent in Right hemisphere) would find further support. More precisely, according to Stuss et al (2005) slow responses are characteristics of patients with Superior Medial prefrontal cortex, and not of all prefrontal patients, therefore it is possible that the dysfunction of children with ADHD, may be more precisely localized, comparing different sets of results.

Following the attention model proposed by Posner and Petersen (1900), the Executive control system was assessed through the number of commission errors on the SART, the errors and the RTs of the Stroop effect in the Counting Number task. Surprisingly, the SART Commission errors were affected by RD not by ADHD. In particular, in the SART, the inhibitory deficit was found in RD-only, in ADHD+RD and in younger ADHD-only children. The results obtained in study 2 helped us to understand that the significant ADHD effect for the commission errors found in study 1 could be due to presence of children with other clinical conditions, such as RD (current study) or Oppositional Deviant Disorder (Van der Meere, Marzocchi & De Meo, 2005). Actually, as proposed above, children with RD were probably more impaired in the inhibition of erroneous responses because they have not automatized digits processing, therefore, in many case they were

unable to rapidly recognize the digits and to suppress the responses. As for the RTs results, it is necessary to run other experiments using choice RT tasks containing inhibitory requests in order to disentangle if the inhibitory deficit is present in children with RD or it is an artifact of their impairment in rapid digit processing.

The second test tapping the Executive control system is the Number Stroop test. In study 2 we refined the experiment to include a baseline condition (Counting Stars) in order to obtain a more reliable measure of the executive control system, subtracting the RTs of Counting Stars from the RTs of Counting Digits. In study 2, the difference of RTs between the Stroop condition and the baseline was considered a measure of the Stroop RT effect because in this task the children had to inhibit an automatic response (naming digits) and to produce a controlled response (counting digits). Moreover, the failure to inhibit an automatic response determined the production of errors, the third variable tapping the executive control system.

The results of the Number Stroop task showed that all children were slower in counting digits than in counting stars (baseline – neutral stimuli): this phenomenon is an example of the Stroop effect. An exception was the fact that RD children counted the digits a bit faster (not significantly) than the neutral stimuli: for the dyslexic children digits and stars were the same and they were not negatively affected by the presence of numbers!

Children with ADHD were affected by the Stroop effect in terms of response speed: they were slower in counting digits than in counting stars. However, children with ADHD+RD produced the highest number of errors on the Stroop task but this result was caused mainly by the presence of their Reading Disorder. Moreover, RD children were slower in counting neutral stimuli, perhaps because of their specific counting impairment, but children with ADHD+RD were not.

The third attentional network (Posner & Petersen, 1990) is the Orienting system. This system was assessed using the Rotated Blackboard test. There were no significant differences between groups. Thus the Orienting system (mainly controlled by the parietal lobe) was spared in ADHD and RD children, as also shown by Swanson et al (1998).

Finally, in the Object naming task the two groups with RD (RD-only and ADHD+RD) were slower than the ADHD-only and the normal control children. This final result extended those obtained by Tannock, Martinussen and Frijters (2000) who showed that children with RD have a deficit in rapid naming.

In conclusion, we try to answer the three questions raised in the introduction:

1) The group with ADHD-only showed an impairment in the Alerting System (Energizing processes of Attention, RTs of SART and Vigilance task) and partly in the Executive Control System (RTs of the Number Stroop Task). RD children were slower in processing of digits both on the SART and on the Vigilance tasks, but it is more likely that they present a deficit in the automatic processing of digits.

2) No children showed an impairment to the Orienting system.

3) Only children with RD-only and ADHD+RD have a deficit in the rapid object naming task. ADHD-only children were not different from normal controls.

4) As far as attentional deficits are concerned the group with ADHD+RD were more similar to RD-only in terms of Energizing processes of Attention (maybe for their slower digit processing), but they were more impaired in the Executive Control system than ADHD-only children.

A possible hypothesis for explaining this complex pattern of results could be that children with a “pure” ADHD are characterized by a pervasive impairment in the Alerting system and in some aspects of the Executive control system, but not specifically in Inhibition. Children with ADHD+RD are characterized by deficits in both the Alerting and partly in the Executive control systems, in particular the Inhibitory processes associated with a difficulty to the automatic lexical access: this latter impairment could be a risk factor that lead them to develop also dyslexia.

Finally, a specific ADHD effect (not present in children with RD) was found only on the RTs of the Stroop effect: children with ADHD were particularly impaired in shifting the type of counting task (from Stars to Digits). Whereas, a specific RD effect (not present in children with

ADHD) was found on the Commission errors of the SART, probably because children with RD were slower to recognize the digits and to stop the inappropriate responses.

Chapter 9

Test of Everyday Attention for Children (TEA-Ch) in children with ADHD and / or RD

9.1 Introduction

Manly, Anderson, Nimmo-Smith, Turner, Watson and Robertson (2001) contributed to the analysis of the attentional problems of children by developing a theoretically based battery (Test of Everyday Attention for Children (TEA-Ch) to assess different types of attentional processes. The main question of these authors was whether the broad views of attention developed predominantly with adults have value in thinking about attention and disorders of attention in childhood. Although it cannot be assumed that the processes of the developing brain correspond closely to those seen in maturity, there are potential advantages if such links can be made. If adult models form a reasonable approximation then both assessment and rehabilitation of attention disorders in children could benefit from the findings of adult studies. In developing the TEA-Ch the aim of the authors (Manly et at al., 2001) was to adapt measures that had proven sensitive in adult attention assessment into game-like assessment tools for use with children between the ages of 6 and 16. As children will vary in many abilities (motor skill, task comprehension, language, and so on), which are implicated in attentional performances, Manly et al (2001) developed a battery aiming to exclude as much as possible such confounding processes, as the problem of "task impurity" has been held to account for the generally low correlations observed between executive measures in adulthood (Burgess, 1997).

Since children might be expected to show greater variability along these non-attentional dimensions (due to the different developmental trajectory of each child and their different life experiences) the challenge may be much greater than for adults. The first approach to meeting this challenge was in the design of the tests. The authors of TEA-Ch (Mainly et al., 2001) aimed to minimise the "demands on memory", reasoning, task comprehension, motor speed, verbal ability, and perceptual acuity while maintaining the demands on the targeted attentional system. To this end, for example, motor speed was controlled for on a visual search task by comparing performance

under high and low attentional demands (in the control task, children had only to circle stimuli and not to select and circle targets among distracters). Where possible, language was avoided in the stimuli or the required responses and the perceptual demands were reduced. Demonstrations and practice trials with correction were used to reduce the impact of task comprehension differences and to try and improve the reliability of performance. Such attempts can only ever have limited success.

The second approach to minimising the impact of "task impurity" was to use Structural Equation Modelling (SEM) in their analysis. This technique is related to the more conventional exploratory factor analysis method but has important differences. In conventional factor analysis, the model is determined in a "bottom-up" fashion from the data, by contrast the SEM tests results according to a top-down hypothesis.

The SEM performed by Manly et al. (2001) revealed the presence of three factors: Selective Attention, Sustained Attention and Attentional Control/Switching. Considering only the five tests selected for our studies, Sky Search loaded on the Selective Attention factor, Opposite Worlds loaded on Attentional Control/Switching factor and Score!, Sky Search DT and Walk Don't Walk loaded on the Sustained Attention factor (for a description of the tests see section on Material).

In addition, Manly et al. (2001) administered the TEA-Ch to 24 ADHD boys (mean age 9.95) and compared their performance with the normative values, matching for Vocabulary or Block Design measures on the WISC-R (Wechsler, 1973). They found that the children with ADHD were significantly worse on several tests, namely: Score!, Walk don't Walk, and Opposite Worlds. The test Sky Search DT, for testing the ability to coordinate two parallel activities, did not differentiate children with ADHD from Normal Controls. Heaton et al (2001) administered the TEA-Ch battery to a group of 63 children with ADHD and to a control group of 23 children, and they partly replicated the results obtained by Manly et al (2001). Finally, Micallef et al. (2001) analyzed the performance of four groups of children: ADHD-only, Learning Disabled (LD-only), ADHD+LD and Controls using an older version of the TEA-Ch, but containing very similar tests to those used in the study published by Manly et al (2001) (assessing only Sustained and Selective

Attention), and they found that the group with LD-only was impaired on the Sustained attention measures, whereas children with ADHD-only were more impaired in Selective attention tasks, in particular where irrelevant stimuli were presented and have to be filtered out. The group with ADHD+LD performed similarly to the ADHD-only group.

The aims of this study were to analyse the pattern of performance of a large sample of children with ADHD on the subtests of the TEA-Ch, that were found to be found sensitive to ADHD in Manly et al.'s (2001) small sample: Score!, Walk don't Walk, Opposite Worlds and Sky Search Dual Task. Moreover, although Sky Search test was not sensitive to ADHD, was included into the battery, in order to administer the Sky Search DT, because it is a combination of Score! and Sky Search).

9.2 Material

a. Sky Search

In this task children were given an A3 sheet depicting rows of paired spacecraft. Four distinctive types of craft were presented, with most pairs being of mixed type. They were instructed to try and find all of the target items, defined by a pair of identical craft, as quickly as possible. Twenty targets were distributed among 108 distractors. Termination of the task was self-determined with the child marking a box in the lower left corner when they had finished. Both speed and accuracy were emphasized. Prior to completing the main test, children first completed a practice A4 sheet to ensure comprehension of target identity and the self completion procedure. In order to control for differences that are attributable to motor speed rather than visual selection, the children then completed a motor control version of the task. The A3 stimulus sheet was identical to that of the Sky Search test with the exception that all of the distractor items were removed. The task therefore consisted of circling all 20 target items as quickly as possible and then indicating completion. Time taken to completion and accuracy were recorded for each part of the test. A time-per-target score was calculated (time/targets found). Subtraction of the "motor control" time per-

target from the more attentionally demanding Sky Search time-per-item produced an "attention" score that was relatively free from the influence of motor slowness or clumsiness. The time required for this test clearly depends upon the speed of an individual child.

b. Score!

The Score! is a 10-item tone-counting measure based on a task originally described by Wilkins et al. (1987). In each item, between 9 and 15 identical tones of 345 ms are presented, separated by silent interstimulus intervals of variable duration (between 500 and 5000 ms). Children were asked to silently count the tones and to give the total at the end–as if they are "keeping the score by counting the scoring sounds in a computer game". If a child was unable to count to 15 or was unable to pass two practice trials (with relatively few tones) the test was not given. The requirement to pass practice items as a way of ensuring task comprehension, checking on possible sensory problems and improving the reliability of the measures, was a feature of each of the tasks. The duration of the test was approximately 5 min 40 s (some variability occurring due to the need to repeat instructions and so forth).

c. Sky Search DT

In the Sky Search DT test children were asked to complete a parallel version of the Sky Search Task which differed only in the location of the targets. As they performed the visual search they were asked to simultaneously and silently count the number of tones presented within each item of an auditory counting task, giving the total at the conclusion of each item. Although the counting task used the same stimuli as the Score! subtest, a regular pacing of one tone per second was used. Following practice, the task and timing were initiated by a countdown played on the tape. The test was ended and timing stopped when the child indicated completion of the visual search component. As it is possible that a child could completely neglect one of the tasks, scores from both measures were incorporated into a total score. Specifically the time taken to find each visual target

was calculated (total time / correctly identified targets)–(a). The proportion of the counting items with correct totals was then calculated (total items correct/total items attempted)–(b). Poor counting performance was then used to inflate the time per-target scores by dividing (a) by (b). Finally, in order to assess the decrement from single task visual search performance, the raw time-per-target score from the Sky Search task was subtracted from this value. To take an example, a child took 89 seconds to complete the task during which he found 19 targets. His time-per-target score was therefore 89/19 = 4.68. During this time he gave correct totals to three of the six counting items he was exposed to. His proportion correct score was therefore 3/6 = 0.5. Dividing the time-per-target score by this proportion inflates his time-per-target score to 4.68 / 0.5 =9.36. In the original Sky Search test, his time-per-target score was 3.2 s. Subtracting this from the dual weighted time-per-target gives the decrement value, 9.36 – 3.2 = 6.16.

d. Walk Don't Walk

In the Walk Don't Walk subtest, children are given an A4 sheet showing "paths" each made up of 14 squares. They are asked to listen to a tape that will play one sound (go tone) if the move to the next square should be made and another (no-go tone) if not. The moves were made by "dotting" each square with a marker pen, the pen being held approximately 2 cm. above the page between each tone. The go and no-go tones were identical for the first 208 ms (329.6 Hz sine tone), the no-go tone being marked by a concluding vocal exclamation ("D'oh!"). The task therefore ideally required children to listen to the entire sound before making their response. The go tones were presented in a regular, rhythmic fashion with the no-go tone occurring unpredictably within the sequence (between the 2nd and 12th steps). Inter-tone intervals began at 1500 ms for item 1. Although held constant within each item, the intervals were systematically reduced with each new item, reaching a minimum of 500 ms at item 20. Two demonstration trials and two practice trials were given before the test items. The dependent variable was the number of items correct out of 20. The total duration of the test items was approximately 6 min 16 seconds.

e. Opposite Worlds

In the Opposite Worlds task, the aim was to make the association as explicit as possible by using the digits 1 and 2 as the stimuli and the words “one” and “two” as the response options. In the task the children were presented with a stimulus sheet showing a mixed, quasi-random array of the digits 1 and 2. In the “Sameworld” condition they were asked to read out the digits aloud as quickly as possible in the conventional manner. The purpose of the “Sameworld” condition was to reinforce the “prepotent” set of naming the numbers in the conventional manner in the context of the test materials, and also to identify any unexpected difficulties a child may experience with the task. In the “Oppositeworld” condition they were asked to say the opposite for each digit (“one” for 2 and “two" for 1) as quickly as possible, inhibiting the prepotent verbal response. In the task, the examiner pointed to each digit in turn, only moving onto the next when a *correct* response was given, thus turning errors into a time penalty. Following practice in each condition, four test pages were run in the order: Sameworld, Oppositeworld, Oppositeworld, Sameworld. The time taken to complete each condition was recorded. Total time for the Oppositeworld condition was taken as the dependent variable.

9.3 Statistical analysis

In order to replicate the study carried out by Manly et al (2001) a first analysis was run considering all children with ADHD (ADHD-only and ADHD+RD) and contrasting them to Controls. A second analysis was carried out to compare children with ADHD-only to Controls in order to analyse the possible specificity of this group of “pure” ADHD. A third analysis was conducted including also children with RD-only and separating children with ADHD-only from those with ADHD+RD. The fourth analysis was a correlation between the five subtests of the TEA-Ch, IQ and reading performance. Finally two exploratory factor analysis were performed considering only controls or only children with ADHD-only and with ADHD+RD.

9.4 Results

1) All ADHD children vs Controls

The results of all children with ADHD and Controls are reported in table 9.1. A MANCOVA (age covaried) run on the five subtests of the TEA-Ch revealed that children all with ADHD (ADHD-only and ADHD+RD) performed significantly more poorly than Controls on Sky Search [$F(1,88) = 10.019$, $p < .01$; $Eta^2 = .104$], Score [$F(1,88) = 22.687$, $p < .001$; $Eta^2 = .209$], on Walk Don't Walk [$F(1,88) = 13.536$, $p < .001$; $Eta^2 = .136$] and on Opposite Worlds [$F(1,88) = 19.008$, $p < .001$; $Eta^2 = .179$], but not on Sky Search DT ($p > .30$). These results partly replicated those obtained by Manly et al (2001), but we have also found a significant difference between all ADHD children and Controls on Sky Search. It should be noted that control children of the present study also performed poorly by comparison with those of Manly et al (2001) on the Walk Don't Walk test, whereas ADHD children performed very similarly to the ADHD sample of study carried out by Manly et al (2001).

2) ADHD-only vs Controls

A MANCOVA (age covaried) run on the five subtests of the TEA-Ch revealed that children with ADHD-only performed significantly poorly on Sky Search [$F(1,73) = 8.805$, $p < .01$; $Eta^2 = .110$], Score [$F(1,75) = 28.098$, $p < .001$; $Eta^2 = .278$], on Walk Don't Walk [$F(1,74) = 9.926$, $p < .01$; $Eta^2 = .121$] and on Opposite Worlds [$F(1,73) = 12.061$, $p < .001$; $Eta^2 = .145$], but not on Sky Search DT ($p > .70$). The results of all children with ADHD, with ADHD-only and Controls are reported in table 9.1.

Table 9.1

Comparison between Controls and ADHD

	Controls N = 37	All ADHD N = 55	ADHD-only N = 38
Sky Search	9.46 (2.66)	7.82 (2.18)	7.75 (2.23)
Score	10.38 (1.92)	7.80 (2.85)	7.53 (2.67)
Sky Search DT	8.14 (3.15)	7.33 (4.35)	7.82 (4.25)
Walk Don't Walk	7.62 (3.66)	4.98 (3.06)	5.16 (3.02)
Opposite Worlds	10.95 (2.00)	8.79 (2.49)	9.08 (2.56)

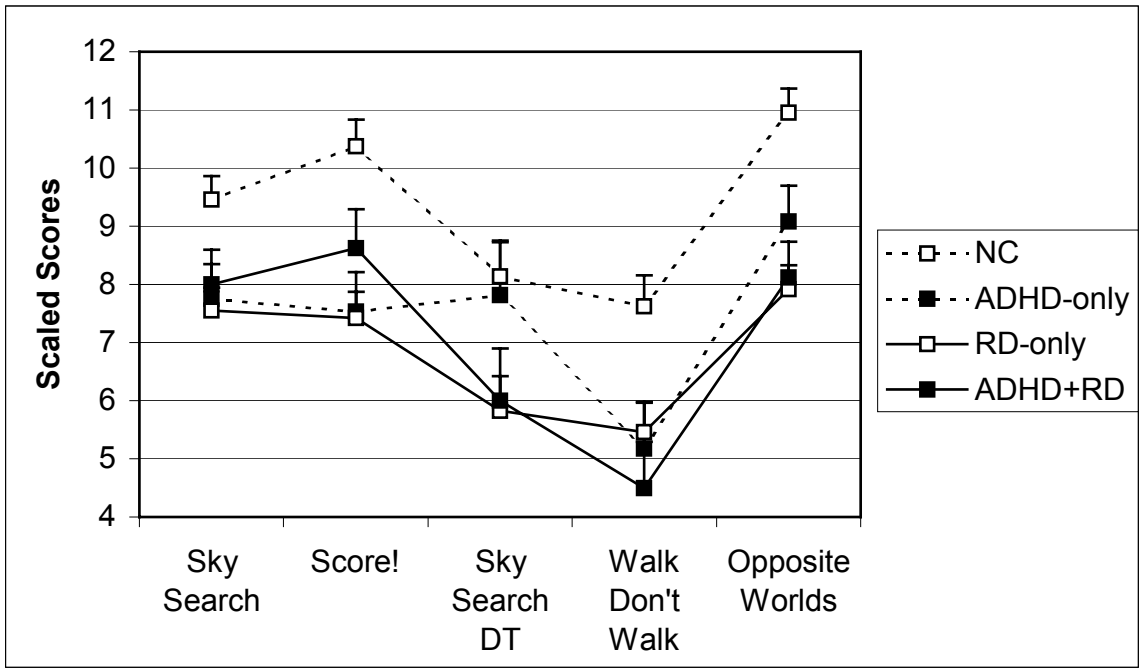
Note: Values are reported in scaled scores.

3) ADHD-only vs RD-only vs ADHD+RD vs Controls

The results of the TEA-Ch on the four groups (ADHD-only, RD-only, ADHD+RD, Controls) are presented in figure 9.1. Values are reported on scaled scores. First of all, just looking at the figure 9.1 we can see that children with RD-only performed significantly poorer than Controls ($p < .01$) on all sub-tests of the short version of the TEA-Ch, but their performance was parallel to that of the control group, therefore their attentional profile did not show any peculiarity. Children with ADHD-only performed very similarly to those with RD-only apart from Sky Search DT where their performance was similar to the performance gave by Controls.

Figure 9.1

TEA-Ch results obtained by Controls, ADHD-only, RD-only and ADHD+RD.



Note: Values are reported in scaled scores. Semi-bars represent Standard Error

A 2 x 2 MANOVA (ADHD by RD) was carried out on the age scaled scores of the five subtests of the TEA-Ch. The only sub-test on selective attention was Sky Search: on this task only the interaction ADHD by RD was significant [$F(1,129) = 5.031$, $p < .05$; $Eta^2 = .040$]. Since the ADHD by RD interaction was significant pairwise comparisons between each clinical group and Controls were performed. The difference between ADHD-only and Controls was significant ($p = .004$) and the difference between RD-only and Controls was significant as well ($p = .001$), therefore the interaction was due to the lack of additive effect: the difference between ADHD+RD and Controls was not significant.

The three tasks loading on the sustained attention factor according to the model proposed by Manly's et al (2001) were: Score, Sky Search DT and Walk Don't Walk. Regarding Score the ANOVA revealed that the interaction ADHD by RD was significant: [$F(1,129) = 14.999$, $p < .001$; $Eta^2 = .109$]. Pairwise comparisons showed that also in this case the interaction was due to the lack of additive effect, and the significant poorer performance of ADHD-only and RD-only children

compared to controls ($p < .001$). The difference between ADHD+RD and Controls was not significant.

On Sky Search DT only the RD effect was significant [$F(1,129) = 6.617$, $p < .05$; $Eta^2 = .055$]. The third task loading the sustained attention factor was Walk Don't Walk test: on it both ADHD and RD effects were significant [$F(1,129) = 7.277$, $p < .01$; $Eta^2 = .057$; $F(1,129) = 4.966$, $p < .05$; $Eta^2 = .039$, respectively]. The only subtest that loaded on Executive / Attentional Control was Opposite Worlds: in this case the RD effect and the interaction ADHD+RD were significant [$F(1,129) = 17.893$, $p < .001$; $Eta^2 = .129$; $F(1,129) = 4.826$, $p < .05$; $Eta^2 = .038$, respectively]. The interaction was due to the lack of additive effect between ADHD and RD and the significant poorer performance of the three clinical groups compared to Controls: ADHD-only ($p = .01$), RD-only ($p < .001$), ADHD+RD ($p = .001$).

So far, all results concerning the five sub-tests of the TEA-Ch have been presented in order to compare Manly et al's (2001) with ours. However the result of the Opposite Worlds test may well be influenced by naming skills, because the measure is the time spent to name digits with an "arbitrary" label (1 instead of 2 and vice-versa). The actual measure represents the capacity of the children to inhibit an automatic response (the digits presented on the card) and to activate another response (the arbitrary label). Therefore the difference, in seconds, between the two conditions "Same-world" and "Opposite-world" represents more faithfully the cognitive process necessary to withhold an automatic response and to active another, arbitrary, one. On this measure ("Opposite-world" – "Same-world") a 2 X 2 ANCOVA was performed in order to compare ADHD and RD. None of the effects were significant ($p > .20$); however a 2 X 2 MANCOVA on the simple measures of "Opposite-world" and "Same-world" revealed a RD effect on both measures: [$F(1,124) = 25.789$, $p < .001$, $Eta^2 = .177$]; [$F(1,124) = 18.499$, $p < .001$, $Eta^2 = .134$], respectively. The effect of ADHD was not significant, but the interaction ADHD by RD was significant on the "Opposite-world" condition [$F(1,124) = 4.197$, $p < .05$, $Eta^2 = .034$], because children with RD-only and children with ADHD+RD performed significantly poorer than Controls ($p < .001$ and $p = .011$,

respectively), and also the additive effect of ADHD and RD was not present. On table 9.2 raw data of "Same-world" and "Opposite-world", in seconds, are presented.

Table 9.2

Opposite Worlds: Raw data on "Same-world" and "Opposite-world" conditions

Variables	ADHD-only (n = 38)		RD-only (n = 39)		ADHD+RD (n = 17)		Controls (n = 37)	
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Same	24.32	(4.51)	29.55	(4.82)	26.93	(5.14)	22.58	(3.45)
Opposite	32.50	(6.40)	36.30	(8.33)	34.91	(8.08)	29.56	(6.11)
Difference (Opp – Same)	8.18	(5.45)	9.35	(7.33)	7.98	(4.80)	6.96	(3.80)

Note: Raw values are corrected by age.

4) Correlation

A correlation between IQ subtests and reading speed with the five subtests of the TEA-Ch was carried out (see table 9.2). For IQ the significant correlations were for Sky Search DT ($p < .01$) and for Opposite Worlds ($p < .05$), for Block Design the correlation with Opposite Worlds was significant ($p < .05$); finally, the reading performance significantly correlated with three subtests of the TEA-Ch, namely Score ($p < .05$), Walk Don't Walk ($p < .05$) and Opposite Worlds ($p < .01$). For the correlation results see table 9.2.

Table 9.2

Correlation between TEA-Ch, WISC-R and Reading.

Sub-tests	**IQ**	**Vocabulary**	**Block Design**	**Reading**
Sky Search	0.043	0.057	0.040	0.132
Score	0.114	0.085	0.159	0.216*
Sky Search DT	0.249**	0.085	0.047	0.159
Walk Don't Walk	0.087	0.174	0.042	0.194*
Opposite Worlds	0.215*	0.149	0.215*	0.387**

Note: * = $p < .05$, ** = $p < .01$.

5) Factor Analysis

Finally, in order to test the proposal by Manly et al. (2001) of the existence of three factors that are loaded differentially on subtests of the TEA-Ch, two exploratory factor analysis (principal components, with the extraction of eigenvalues over 1, with VARIMAX rotation) were carried out. The first factor analysis included only control children. The second factor analysis considered all children with ADHD (this differentiation was made because of the massive effect of RD). The exploratory factor analysis is less theoretically based than Structure Equation Model but due the absence of some subtests of the entire TEA-Ch it has been decided to apply this type of analysis.

The factor analysis run on Controls showed that two factors were obtained (explaining 64.39% of the variance): factor 1 includes Sky Search, Walk Don't Walk and Opposite Worlds tasks, factor 2 includes Score! and Sky Search DT. The interpretation of these results are not straightforward because factor 2 included both tasks that are related to the ability to keep counting of sounds, whereas the factor 1 includes all other tasks, very different from each others requiring visual search, motor inhibition and rapid naming.

The factor analysis run on the children with ADHD produced three factors (71.94% of the variance being explained): factor 1 includes Sky Search and Opposite Worlds, factor 2 includes

only Sky Search DT and factor 3 includes Walk Don't Walk and Score. The results of the factor analysis are reported in table 9.3.

Table 9.3.

Factor Analysis of the TEA-Ch.

Sub-tests	*Controls*		*All ADHD*		
	Factor 1	**Factor 2**	**Factor 1**	**Factor 2**	**Factor 3**
Sky Search	.828		.807		
Score!		.603			.715
Sky Search DT		.886		.876	
Walk don't walk	.679				.726
Opposite Worlds	.838		.750		

9.5 Discussion

In this study we used a short version of the TEA-Ch found to be sensitive to ADHD according to the study published by Manly et al. (2001). We included the following subtests: Sky Search, Score, Sky Search Dual Task, Walk don't Walk and Opposite Worlds. We administered these subtests to one hundred thirty-one children divided in four groups: ADHD-only, RD-only, ADHD+RD and Controls. This is the first study, to our knowledge, that used the TEA-Ch to assess the attentional profile of children with RD-only or ADHD+RD.

One of the aims of this study was to replicate the findings published by Manly et al (2001) using a short version of the TEA-Ch. Manly et al showed that children with ADHD (not differentiating those with or without Reading Disability) are impaired on Walk Don't Walk, Score and Opposite Worlds; no difference was found between ADHD and Controls on Sky Search and Sky Search DT.

In this study four groups of children were involved but, in order to replicate the study of Manly et al (2001) two different types of analysis have been performed. The first type of analysis was run combining children with ADHD-only and ADHD+RD into a single group of all-ADHD. Children with ADHD were collapsed in order to have a group with ADHD with similar characteristics than that Manly et al. studied.

As far as the first set of analysis, our study partly replicated the same results obtained by Manly et al (2001) although these authors used a different methodology of comparison: they tested a group of 24 boys (mean age 9.95) with very low performance on Vocabulary (scaled score 5.42) and Block Design (scaled score 6.96) of the WISC. Then they chose a control group, matched to children with ADHD for their performance on Vocabulary or Block Design, but not matched for both measures. Therefore it is not known if the group of children with ADHD had an average IQ and if the control group was really matched for general cognitive abilities. However, with a better refined sample, the differences we found between ADHD and Controls in the present study were very similar to those obtained by Manly et al (2001) because children with ADHD were impaired on the following sub-tests of the TEA-Ch: Sky Search, Score, Walk Don't Walk and Opposite Worlds.

The second set of analysis was performed considering also children with RD-only and, among the group with ADHD, those with only ADHD from those with ADHD+RD. In this way it is possible to separate the role of ADHD or RD in causing a particular performance on the TEA-Ch. Using this type of analysis the present results demonstrated that children with RD-only showed impaired performances on all the five sub-tests of the TEA-Ch (including also Sky Search DT). The effect of RD was significant for Walk Don't Walk, Sky Search DT and Opposite Worlds. These tests are very different from each other and they measure different attentional processes: both Sustained and Executive Attention (not Selective Attention). This result is not surprising because Micallef et al. (2001) claimed that children with Learning Disabilities are mostly impaired in

tasking tapping sustained attention, whereas children with ADHD are more impaired on selective attention tasks.

The effect of ADHD was significant only for Walk Don't Walk, which is the only task that also includes a motor inhibition component, associated with auditory sustained attention processes. Finally the interaction ADHD by RD was significant for Sky Search, Score and Opposite Worlds. In this case all the three types of attentional processes are included (Selective, Sustained and Executive). The interaction on these three tasks were due to the absence of any additive effect of the combined presence of both ADHD and RD; the performance of the group with ADHD+RD was not worse than the performance of children with ADHD-only or RD-only. From inspection of figure 9.1 it is clear that the group with ADHD+RD gave a level of performance very similar to that given by children with RD-only, therefore their attentional skills are very similar to the those of children with RD-only.

Another issue is the relative independence of the TEA-Ch tests from other psychological processes. Actually, the performance on the tasks included into the TEA-Ch are not really free from other cognitive characteristics because they strongly tap on: perception and visual search (Sky Search), counting skills and phonological memory (Score), motor control, impulsiveness and ability to follow a rhythmic sound (Walk Don't Walk), and access to lexicon (Opposite Worlds). Therefore we cannot be sure that the poor performance of the RD-only group is essentially due to their poor attentional skills: for instance the correlation between Opposite Worlds and Objects rapid naming (see chapter 6) is significant ($r = 0.369$, $p < .001$). In order to disentangle these issues it is necessary, in future researches, to control more carefully the above described processes by including other tasks that do not stress attention but analyze only the non-attention processes.

According to our results, excluding Sky Search DT, children with ADHD-only and RD-only are comparable in their attentional skills. This is not an obvious result because children with RD may have problems in the cognitive activities implicated in the execution of many tasks of the TEA-Ch (visual search, counting skills, phonological memory, following a rhythmic sound and rapid

digit naming), but children with ADHD may have problems in the execution of these tasks because of their difficulty in self-regulating their effort, avoiding distractions, and inhibiting impulsive responses. Actually these post-hoc interpretations are speculative because this battery did not give us the possibility to control for other cognitive processes implicated in the execution of the tasks. Thus in the Walk Don't Walk, children could produce an error because of difficulty in following rapid sounds (presumably impaired in children with RD) or in inhibiting incorrect motor responses (presumably impaired in children with ADHD).

In summary, this battery revealed mainly that children with ADHD-only and RD-only performed similarly and the additive effect of these two conditions was not present in children with ADHD+RD.

In order to give a plausible interpretation of these set of results, and mainly concerning the lack of an additive effect, we can postulate that, in line with the literature, the similar level of impairment in the performances of children with ADHD-only or RD-only be due to different reasons (different cognitive impairments in the two disorders) and that the these two sources of impairments are not summed in children with ADHD+RD. However, it is possible that the etiology of children with ADHD+RD is different from those of the two pure disorders and that their most pronounced impairment is not observable in attentional activities, or at least, their impairments are more pronounced on other cognitive activities, such as Inhibition, Memory, Rapid verbal processing (see chapter 12 for the analysis of each cognitive process).

To be specific, a possible interpretation of the similar performance of children with ADHD-only and RD-only on Sky Search is that children with ADHD-only may have difficulty in this task because they are not able to use their time efficiently to detect targets (Marzocchi & Cornoldi, 1998), whereas children with RD-only has also been suspected that may be impaired because of a visuo-spatial attention deficit (Facoetti, et al., 2003). The similar performance on the Score test may be caused by the difficulty of ADHD-only children to maintain their energizing attention on the task (Sergeant et al., 1999) and children with RD-only may be impaired because of their phonological

working memory (see Vellutino et al., 2001) on automatic counting skills (Nicholson & Fawcett, 1999). On the Sky Search DT a RD effect was significant and in this case children with ADHD-only were not impaired. The normal performance of children with ADHD-only may be due to the fact that during the execution of the dual task they were more activated and stimulated to perform better than on the other tasks. This interpretation fits with the proposal that there is an energizing attentional deficit in children with ADHD proposed by Sergeant and colleagues (1999) and supported in chapter 8.

The similar performance on Walk Don't Walk of the two pure disorders may, again, be caused by different deficits: children with ADHD-only may be impaired because of their difficulty to inhibit inappropriate motor responses (Barkley, 1997) whereas children with RD-only may have problem to analyze rapid sounds (Tallal, 1980; 2004). However, the hypothesis proposed by Tallal has been criticized by several authors (e.g. see White et al., 2006) who claim that no auditory deficit is present in children with RD, and that a phonological impairment is the key problem observed in dyslexics. In reply, Tallal (2004) argues that 50% of children with dyslexia presented, some years before, with Language Learning Impairment (LLI; and one of the critical feature of children with LLI is auditory deficit. For this reason, it not possible, at the moment, to exclude that in this RD-only group some children may be present with signs of LLI which could have affected the performance on the Walk Don't Walk. Further studies must clarify whether children with RD are really impaired on the Walk Don't Walk task, and if so, it is necessary to analyse the type of errors.

Actually in this case (Walk Don't Walk) the group of children with ADHD+RD was impaired as well, and the two effects (ADHD and RD) were significant therefore it is likely that children with ADHD+RD are more impaired on attentional tasks that require also the inhibition of incorrect responses.

Finally, a similar performance of the three clinical groups was found concerning the Opposite Worlds task. In this test rapid digit naming is required so that it is possible that children with RD (RD-only and ADHD+RD) were impaired because of difficulty in rapidly processing

verbal stimuli, as found in chapter 8 concerning the speed of responses to the SART stimuli. Moreover, this task requires the capacity to inhibit an automatic response (the digits on the card) and activate an opposite response (as in the Stroop task). It is plausible that the deficit observed in children with ADHD-RD may be caused by their difficulty to rapidly shift from one type of response to another, as observed in the Number Stroop task in chapter 8.

In order to detect if attentional tasks are related to IQ or reading speed performance a correlation analysis was carried out but the only significant correlation between IQ and TEA-Ch was on Sky Search DT. The reason for this significant correlation is due to the strong correlation between Arithmetic (subtest of the WISC-R) and Sky Search DT ($r = .30$, $p < .01$), because the correlations between Sky Search and the other subtests of the WISC-R were not significant. Thus it is possible that this correlation between Sky Search DT and our estimation of IQ is merely an artefact due to the use of some, not all, subtests of the WISC-R, in particular Arithmetic that is sensitive, not only to arithmetical skills but also to attentional difficulties (Mayes & Calhosun, 2002).

Finally two factor analyses were performed in order to test if the TEA-Ch assesses three different attentional processes as proposed by Manly et al (2001) (Selective, Sustained and Executive Control). The factor analysis carried out on the control groups revealed that Sky Search, Walk Don't Walk and Opposite Worlds loaded on one factor (and not three as obtained by Manly et al.), and Score and Sky Search DT loaded another factor. These two latter tasks have in common that the performance is mediated by sustained auditory attentional abilities. The second factor analysis was only run including ADHD children: in this case, three factors were obtained, factor 1 includes Sky Search and Opposite Worlds (two tasks that required rapid visual scanning), factor 2 includes only Sky Search DT and factor 3 includes Score and Walk Don't Walk.

In conclusion the TEA-Ch battery is able to discriminate both children with ADHD or with RD from Controls but it is not sensitive enough to discriminate these two clinical conditions. This effect could be due to problem of task impurity that the authors of the TEA-Ch did not solve

completely because all tasks necessarily required the execution of other cognitive processes that could influence the attention performance.

Chapter 10/a.

Working Memory in children with ADHD assessed by an N-back task

10/a.1. Introduction

This experiment was performed as a part of study 1 (1999). In order to find the core memory deficit in children with ADHD most researchers have focused their analysis on the functioning of the central executive system of the working memory (Baddeley, 1986) and on the use of learning strategies. N-back is often used as a measure of executive working memory processes The hypothesis is that children with ADHD have poorer memory performance due their executive control impairment and their inability to efficiently apply learning strategies. The results of researches with ADHD children on memory tasks are controversial: some studies found significant different between ADHD and controls (Roodenrys, Koloski & Grainer, 2001; Cornoldi, Marzocchi, Belotti, Caroli, De Meo & Braga, 2001) but some did not (Stevens, Quitter, Zuckerman & Moore, 2002; Dewey, Kaplan, Crawford & Fisher, 1998; Kuntsi, Oosterlaan & Stevenson, 2001). For all details about these studies, see chapter 3, paragraph 5.4.

The aim of this study was to analyse the working memory functioning in children with ADHD administering an n-back task. To my knowledge, this is the first study in which an N-back task, presenting digits, has been used in children or in ADHD patients. Therefore there are no other papers to compare with our study, however the presence of working memory deficit in ADHD is still debated in the literature (see paragraph 2.3 of the Introduction).

10/a.2. Material

The children were presented with 216 digits, one every two seconds in three different blocks (72 digits x 3 blocks) corresponding to levels of difficulty (0, 1 and 2 back). The numerals were presented on a screen (size: 11") at 0.70 cm distance, and 20 digits (of 72) were preceded by a tone. After the tone, 50% were valid trials and 50% were invalid trials. The validity depended on the

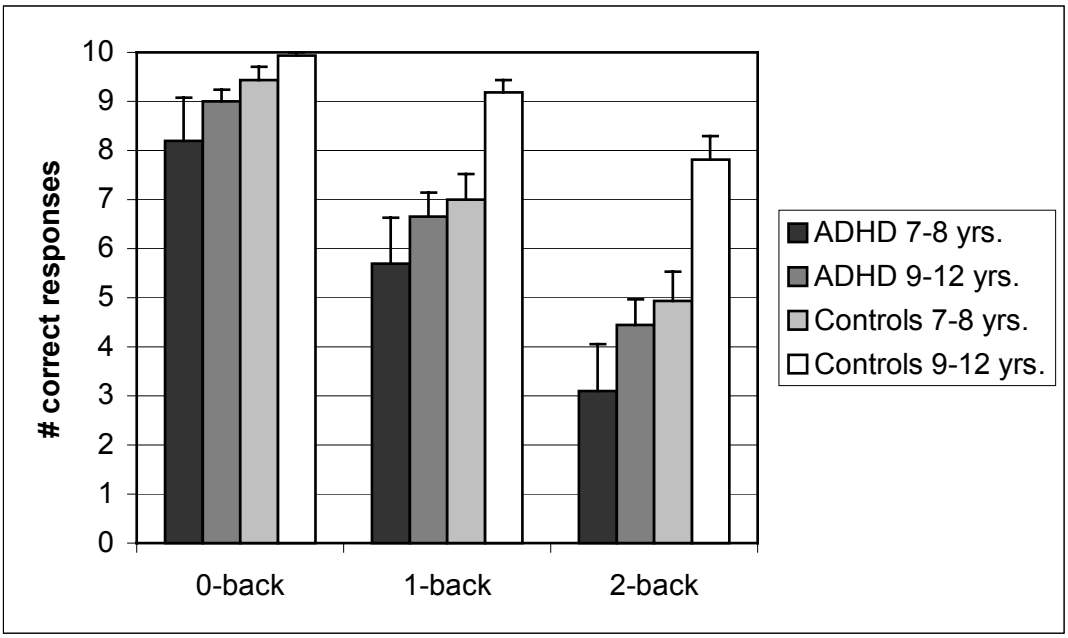
stimuli after the tone: at the first level (0 back) the children had to press a key of the keyboard only if, after a tone, they saw a "5" (after the tone 50% of the stimuli were "5" and 50% were other digits). In this condition, participants had to inhibit their response; if they did not press a key, a correct refusal was recorded. At the level 1-back, the children were asked to press a key only when the numeral presented after the tone was identical to that one presented just before the tone. At the 2-back level, the participants were asked to press the key only when the numeral presented after the tone was identical to that one presented two trials before the tone. For each level, three measures were taken: correct responses, commission errors (when a child press a key but the stimulus was not a target) and reaction times of correct detection of target. The summation of commission errors and correct responses were higher than 10 because half of the tones were presented just after a target and half of the tones are presented just after a non-target.

10/a.3. Results

The results on the number of correct responses are shown in figure 10/a.1.

Figure 10/a.1

N-back working memory task: number of correct responses.



Note: 0-back = the Ss. must respond if a "5" appeared after a tone. 1-back = the Ss. must respond if the number after the tone is identical to those presented before the tone. 2-back = the Ss. must respond if the number after the tone is identical to those presented two numbers before the tone. Semi-bars represent standard error. The maximum value is 10.

A 2 X 3 ANCOVA (ADHD x n-back level, age was covaried) was computed on the number of correct responses. There were significant effects of both ADHD and age [$F(1,59) = 23.910$, $p < .001$, $Eta^2 = 0.255$; $F(1,59) = 11.004$, $p < .01$, $Eta^2 = 0.185$, respectively]. The effect of n-back level [$F(2,59) = 17.547$, $p < .001$, $Eta^2 = 0.226$] and the interaction ADHD by n-back level [$F(2,59) = 8.235$, $p < .01$, $Eta^2 = 0.121$] were significant as well. The interaction ADHD by n-back level was due to the linearly increasing differences between the ADHD and the normal control group across the load of the task.

In fact, the N-back task did not require only working memory skills because children had to attend very carefully the stimuli, therefore it is necessary to determine whether their poor performance was due to a deficit of attention or motivation to follow the rapid presentation of the stimuli, or for a true inability to keep (and mostly update) in memory the different digits presented. For this reason, a second 2 x 2 ANCOVA mixed design was performed: subject group was the

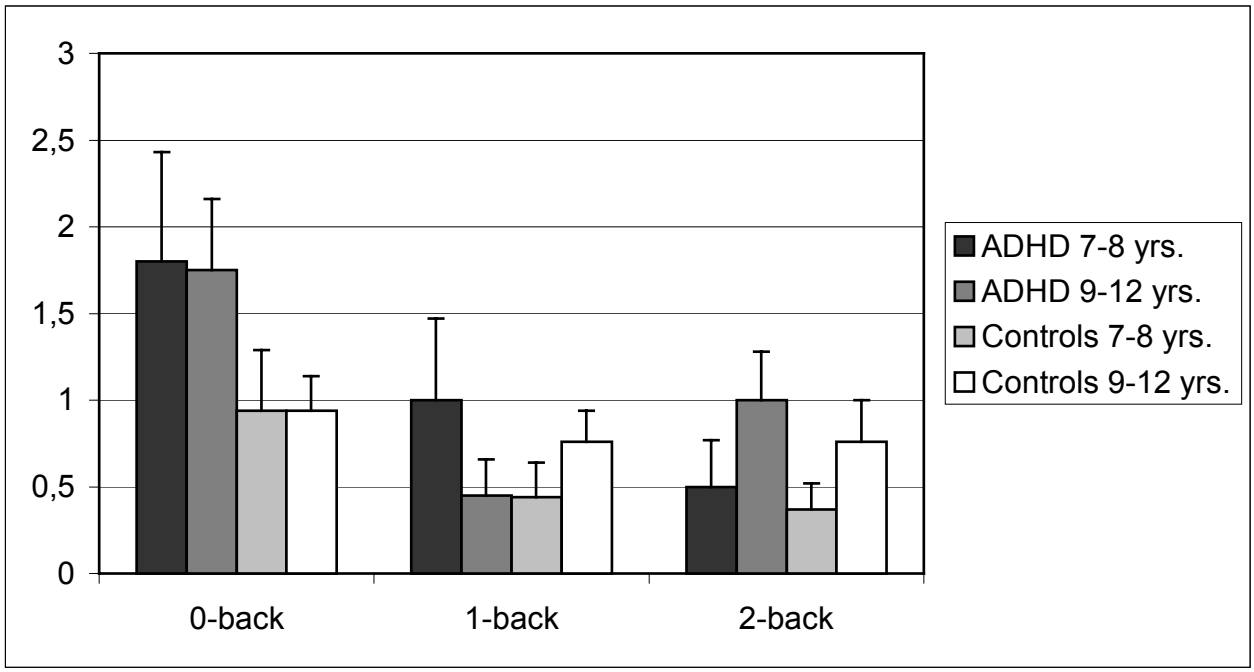
between group factor, 2 n-back levels (1-back vs 2-back) was the within group factor, considering age and number of correct responses at 0-back level as covariates, in order to partial out the effect of attending stimuli. The 0-back level was used a covariate because that condition did not require working memory, since children were asked to press a key only if the digit, just after the tone, was "5" or not.

The covariation by 0-back level was highly significant [$F(1,59) = 22.337$; $p < .001$, $Eta^2 = 0.275$] confirming our hypothesis that the performance is highly affected by attention variables; however the effect of ADHD remained significant [$F(1,59) = 12.436$; $p < .01$, $Eta^2 = 0.174$], confirming also that children with ADHD showed a working memory impairment.

Another variable is the number of commission errors: the subject pressed a key but the digit presented just after the tone did not correspond to a target. The results on the number of commission errors are reported on figure 10/a.2. In this case, only the n-back level effect was significant [$F(2,59) = 4.423$; $p < .05$, $Eta^2 = 0.069$], because all children made fewer commission errors at the 1-back level and at the 2-back level than at the 0-back level ($p < .01$). The ADHD effect and the interaction were not significant.

Figure 10/a.2

N-back working memory task: number of commission errors.

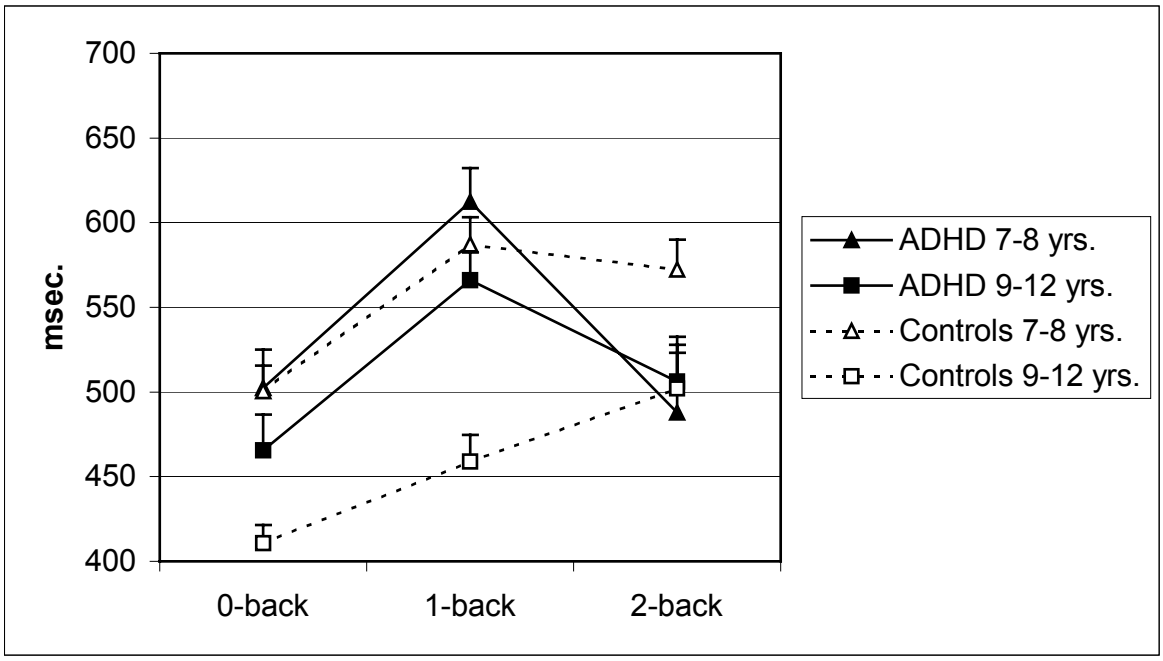


Note: 0-back = the Ss. must press a key if a "5" appeared after a tone. 1-back = the Ss. must press a key if the number after the tone is identical to those presented before the tone. 2-back = the Ss. must press a key if the number after the tone is identical to those presented two numbers before the tone. Semi-bars represent standard error.

The results on the RTs of the correct responses are reported on figure 10/a.3.

Figure 10/a.3

N-back working memory task: RT of correct responses.



Note: 0-back = the Ss. must press a key if a "5" appeared after a tone. 1-back = the Ss. must press a key if the number after the tone is identical to those presented before the tone. 2-back = the Ss. must press a key if the number after the tone is identical to those presented two numbers before the tone. Semi-bars represent standard error.

The same 2 x 3 ANCOVA was applied to the RTs of correct responses: the age effect was significant [$F(1,56) = 18.044$, $p < .001$] because younger children were slower than older children in particular at 0-back level and 1-back level. The main ADHD effect was not significant. The quadratic effect of n-back level was significant [$F(1,56) = 11.03$, $p < .01$, $Eta^2 = 0.172$], because the RTs were higher in the 1-back level than in the 0-back and in the 2-back levels ($p < .001$). The interaction n-back level by ADHD was significant: both the linear [$F(1,56) = 4.478$, $p < .05$, $Eta^2 = 0.073$] and the quadratic effect [$F(1,56) = 16.368$, $p < .001$, $Eta^2 = 0.223$]. The interaction was due to the linear increase of RTs in the normal controls group from 0-back to 1-back level ($p < .01$), but not from 1-back to 2-back level. However, the RTs of ADHD children increased from 0-back to 1-back level ($p < .001$) but decreased from 1-back to 2-back levels ($p < .01$).

10/a.4. Discussion

In this study we analysed the performance of children with ADHD administering a working memory n-back task in which children were asked to look at a screen and memorize series of digits (3 blocks of 72 stimuli). The subjects had to keep in mind the digits presented on the screen and pressing a key in three different conditions: 1) they have to press a key after a tone only if the last digit was "5" (0-back condition), 2) if the last two digits were identical (1-back condition), 3) or if the last digit was identical to the digit seen two positions before (2-back condition).

Children with ADHD gave fewer correct responses at each level, but the differences between ADHD and controls increased across the three levels of memory load. This result showed that children with ADHD had more difficulties in detecting a target (the digit 5) before a tone: this result was interpreted in terms of difficulty to attend a stimulus, rather than a working memory deficit. This interpretation is based on the fact that, in the 0-back condition, children did not have to memorize a series of digits but they were asked to press a key if the digit presented on the screen, just after the tone, was "5" or not. Since this condition, 0-back, was not considered a measure of working memory performance but it is more related to attention, we carried out an ANCOVA on the performance of the two working memory levels (1-back and 2-back), and we found the covariation was significant, meaning that the task required a significant attention load, but more interestingly, the effect of ADHD still remained statistically significant. Thus children with ADHD present a working memory impairment because their performance at 1- and 2-back levels was still poorer compared to the performance of normal controls.

From inspection of figure 10.1/a it is possible to observe that only older controls were able, at 2-back level, to give responses above the chance level (5 correct responses) whereas younger controls and ADHD children were not able to reliably perform the task. However, the performance of the subjects at 1-back level was more reliable than their performance at 2-back level because the number of correct responses were: Controls = 8.12, ADHD = 6.33.

Considering also the RTs of correct responses, a quadratic effect was found: because ADHD children and younger control children became slower from 0-back to 1-back and they became faster at 2-back. This means that the speed of responses was not a reliable variable because the difficulty of the task increased from the 1-back to 2-back, therefore it is not plausible that children became faster if they tried to do the task carefully. They became faster because they were not able to carry out the task in the most difficult condition (2-back).

On the other hand older control children became slower from 0-back to 1-back to 2-back in a linear fashion. This is a confirmation that only older controls were able to perform the most difficult condition of the n-back task.

Although we cannot consider reliable the performance of the children at 2-back level (because ADHD children did appear to give up), we think that the performance at 1-back level is reliable. Given that, we can confirm that children with ADHD present a working memory deficit because their performance at 1-back level was significantly poorer than the performance of controls, on both accuracy and speed of responses.

According to a meta-analysis published by Martinussen et al (2005) the standardized mean differences between ADHD and Controls was high on tasks requiring the use of the Central Executive (Baddeley, 1986) to manipulate spatial information (ES = 1.06). Whereas the standardized mean difference between ADHD and Controls on tasks requiring the active manipulation of verbal information was lower (ES = 0.56). Thus, for Martinussen et al (2005) children with ADHD have more working memory problems if they have to actively maintain spatial than verbal information.

The current n-back required the active maintenance of a series of digits in working memory, therefore processing of verbal material was necessary. In the current study the effect size [(Mean ADHD – Mean Controls)/ mean SD] is 0.80 considering the correct responses at 1-back, and 0.94 at 2-back. This result is not perfectly coherent with the results of the meta-analysis published by Martinussen et al (2005) because the difference between our two groups was almost double,

compared to the mean difference of other 13 studies. It must be noted that in our task the stimuli were visually presented, therefore it is possible that not only verbal working memory was involved but also visual (although not spatial) working memory. If this peculiarity is kept into account, and also the studies concerning the active manipulation of visuo-spatial information are included, the effect size of the difference between our two groups is in the range proposed by Martinussen et al (2005).

The number of commission errors (when a child pressed a key when the stimuli was not a target) discriminated ADHD from controls only at the 0-back level but not at 1- or 2-back levels (when the memory load increased). This means that children with ADHD produced more incorrect responses when the task was relatively easy; after the first block they became more cautious and they did not press a key when they were not sure of the response. This result could be interpreted in terms of inhibitory deficit: if the task is relatively easy ("press a key after a tone only if the digit is 5") children with ADHD have difficulties to withhold incorrect responses, but if their responses are related to working memory process, their inhibitory deficit is not so pervasive to be observed in all conditions, and children with ADHD tend to prefer not to respond if they were not sure, than responding in case of doubt.

In conclusion this version of n-back is too difficult for children with ADHD aged from 7 to 12 years, because the 2-back condition was not carried out appropriately (responses at chance level). However at 1-back level (when the children had to remember only the last digit seen before the tone) children with ADHD performed more poorly than controls. In this case both groups tried to do of their best and the performance on the task is reliable. Although the task has some limitation (above described) from this restricted set of data we can conclude that this group of children with ADHD presented a working memory deficit.

Chapter 10/b.

The use of learning strategies in children with ADHD and / or RD

10/b.1. Introduction

This experiment was performed as part of the study 2 and involved four groups of children: ADHD-only, RD-only, ADHD+RD and Controls.

Many researches showed that frontal brain regions play a significant role in supporting two executive aspects of memory: organizational strategy use in episodic memory (Gershberg & Shimamura, 1995; Incisa della Rocchetta & Milner, 1993; Moscovitch, 1992; Stuss et al., 1994; Fletcher et al., 1998) and manipulation of information in working memory (Casey et al., 1995; Jonides et al., 1993; Luciana & Nelson, 1998). Frontal brain regions, however, mediate strategic control processes that facilitate the efficient organization of complex information, which in turn facilitate the formation of robust memory traces (Moscovitch, 1992; Moscovitch & Umiltà, 1990, 1991). This model has been supported by neuroimaging findings of frontal cortex involvement in long-term encoding and retrieval (Buckner & Petersen, 1996; Nyberg, Caeza, & Tulving, 1996; Petrides, 1995). According to Fletcher et al. (1998) left prefrontal cortex is mainly involved in the encoding stage of memorization, where right dorsolateral prefrontal cortex mainly control the retrieval phase.

As far as the use of learning strategies is concerned some researches found that children with ADHD are not able to apply efficient strategies to improve their memory performance (O'Neill & Douglas, 1991; Douglas & Benezra, 1990; Kramer, Knee & Delis, 2000; Sechi, Corcelli & Levi, 1999; Cornoldi, Barbieri, Gaiani & Zocchi, 1999). Other studies did not find any difference between ADHD and controls (e.g. Mahone, Koth Cutting, Singer & Denckla, 2001).

Cornoldi, Barbieri, Gaiani and Zocchi (1999) administered to ADHD and control children a 4 trial-free recall task of categorizable and partially repeated material (16 pictures in 4 matrixes). ADHD subjects recalled fewer correct items and made more interference errors. However children

with ADHD did not differ from Controls on the knowledge of efficient learning strategies, assessed through a questionnaire on metacognitive knowledge. The differences between ADHD and controls did not disappear even when they were informed about the use of appropriate memory strategies (semantic clustering). ADHD children performed similar to controls only when they were assisted on the use of strategies. The authors (Cornoldi et al 1999) concluded that children with ADHD were able to recognize efficient memory strategies (metacognitive knowledge) but they were impaired in the correct application of memory strategies (executive process).

The aims of this study were to assess episodic memory and the use of learning strategies in children with ADHD and / or Reading Disability: in particular we were interested to analyze if they were able to use semantic clustering strategies, during the retrieval phase, for enhancing a better recall; and finally we were interested to evaluate their capacity to control interferences.

10/b.2. Material

In this study, children were presented with 3 lists of 24 partially categorizable words: 8 animal nouns, 8 fruit nouns and other 8 concrete nouns different from the other two categories, in order to see if they were unable to use semantic clustering strategies. A cluster is considered a combination of two or more items belonging to the same category (in this case Animals or Fruits) recalled in chunk. Moreover, in order to analyse the ability to use the chunking strategy the proportion of words (fruits + animals) recalled in clusters over the total recalled words was calculated. These variables were obtained in order to analyse specifically the chunking strategies without being affected by storage capacity differences between the subjects. The lists 2 and 3 contained half of the words presented in lists 1 and 2, respectively, and half of the words were new because we were interested to see whether children were able to control interferences. In this case, three dependent variables were considered: Proactive Interference (when a child recalled words presented in a preceding list), Repetitions (when a child recalled the same item more than once) and Extra-list Intrusions (when a child recalled a word presented in none of the lists).

The examiner read the 24 words of each list and then let the children memorise the list for 90 seconds. Then the children were asked to recall as many words as possible in the order s/he preferred (free recall). In the first list the material was not semantically structured and no help was given to the child. In the second list, the material was unstructured but the examiner told children to try to make semantic clusters in order to recall more words. In the third list the words were blocked into categories and the examiner reminded to children to use semantic clusters in order to recall more words. The material is reported on appendix 10.1.

10/b.3. Results

The number of total words recalled, words recalled in clusters, words recalled not in clusters (fruits and animals) and other words not belonging to any specific category are reported in table 10/b.1.

Table 10/b.1 Strategic Free Recall Task.

Words recalled.

Variables	ADHD-only (N = 38)		RD-only (N = 39)		ADHD+RD (N= 17)		NC (N = 37)	
Total Words	Mean	*(S.D.)*	*Mean*	*(S.D.)*	*Mean*	*(S.D.)*	*Mean*	*(S.D.)*
List 1	9.17	(4.12)	8.10	(3.98)	7.45	(3.99)	11.20	(4.51)
List 2	9.39	(4.23)	8.13	(4.01)	7.18	(4.03)	10.77	(4.36)
List 3	9.20	(4.05)	7.85	(4.10)	8.01	(4.06)	11.16	(4.60)
Fruits + Animals in Clusters								
List 1	4.01	(2.69	2.69	(2.67)	2.86	(2.80)	4.55	(2.63)
List 2	5.27	(2.84)	4.41	(2.81)	3.75	(2.76)	5.97	(2.76)
List 3	5.15	(2.20)	5.49	(2.18)	5.16	(1.91)	7.42	(2.14)
Fruits + Animals NOT in Clusters								
List 1	2.66	(1.96)	3.20	(1.94)	2.92	(1.88)	3.62	(1.91)
List 2	1.83	(1.94)	1.81	(1.92)	1.47	(1.31)	2.10	(1.88)
List 3	1.36	(1.15)	0.64	(1.14)	0.90	(1.20)	0.74	(1.12)
Other words								
List 1	2.50	(1.44)	2.21	(1.42)	1.67	(1.03)	3.03	(1.40)
List 2	2.29	(1.30)	1.91	(1.29)	1.96	(1.71)	2.70	(1.26)
List 3	2.69	(1.66)	1.72	(1.65)	1.95	(1.80)	3.00	(1.62)

Note. Values are corrected by age.

Three 2 x 2 MANCOVAs (ADHD by RD, age covaried) have been carried out considering the following variables of the three lists: Total Words, Words Recalled in Clusters, Words Recalled Not in Clusters, Other Words, and the difference between Words Recalled in Clusters – Words Recalled Not in Clusters. The decision to run three different MANCOVAs is due to the fact that for each list the instructions were different, therefore the variables of each list were independent. The

first MANCOVA performed on the List 1 showed that the RD effect was significant for Total Words [$F(1,128) = 24.302$, $p < .001$, $Eta^2 = .163$], Words Recalled in Clusters [$F(1,128) = 8.5008$, $p < .01$, $Eta^2 = .065$], and for Other Words [$F(1,128) = 9.666$, $p < .01$, $Eta^2 = .073$] (children with RD-only and ADHD+RD recalled fewer Words in Clusters and Other Words than children with ADHD-only and Controls). The ADHD effect and the interaction ADHD by RD were not significant.

The second MANCOVA carried out on List 2 demonstrated that only the RD effect was significant for Total Words [$F(1,128) = 27.773$, $p < .001$, $Eta^2 = .182$], Words Recalled in Clusters [$F(1,128) = 8.166$, $p < .01$, $Eta^2 = .062$] (also for List 2, children with RD-only and ADHD+RD recalled fewer Words in Clusters than children with ADHD-only and Controls). The ADHD effect and the interaction ADHD by RD were not significant.

The third MANCOVA performed on List 3 showed that the ADHD effect was significant for Total Words [$F(1,128) = 20.606$, $p < .001$, $Eta^2 = .142$], Words Recalled in Clusters [$F(1,128) = 9.470$, $p < .01$, $Eta^2 = .071$] and for the difference between Words Recalled in Clusters minus Words Recalled Not in Clusters [$F(1,128) = 10.066$, $p < .005$, $Eta^2 = .076$] (children with ADHD-only and ADHD+RD recalled fewer Words in Clusters and more Words Not in Clusters than children with RD-only and Controls). The RD effect was significant only for Other Words [$F(1,128) = 10.918$, $p < .01$, $Eta^2 = .082$]. The interaction ADHD by RD was not significant.

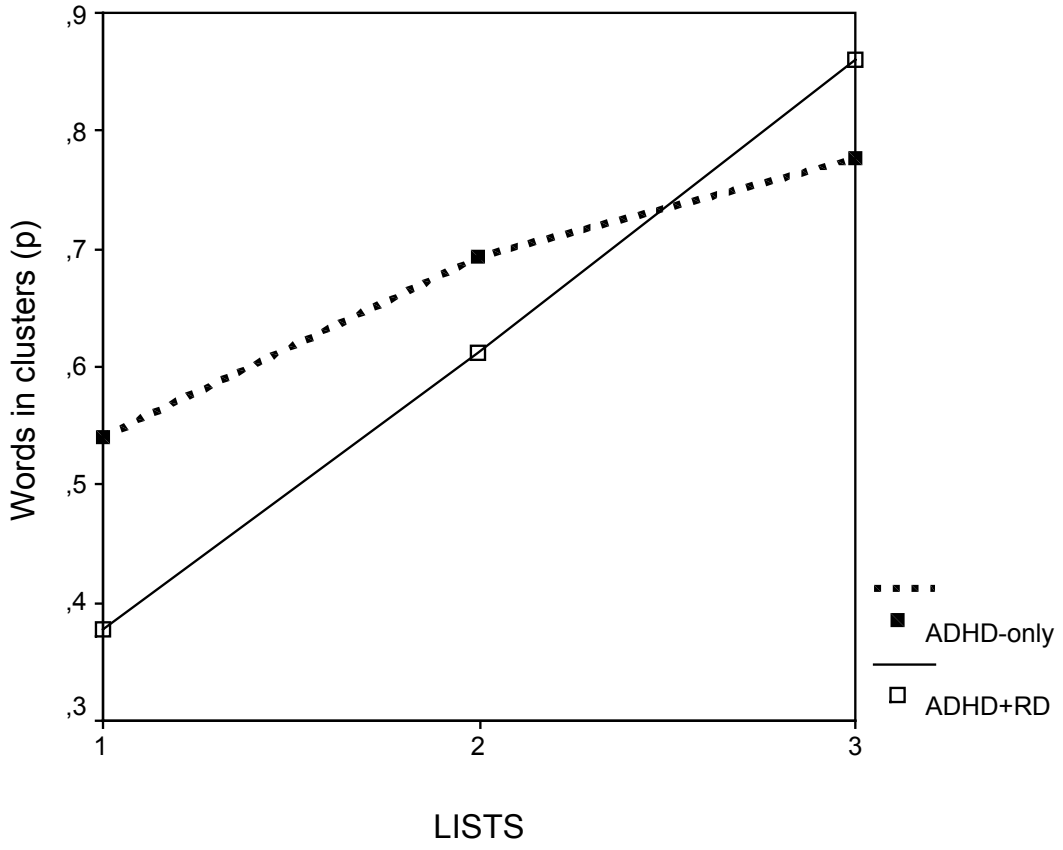
The last ANOVA was performed on the Total number of words recalled in the three lists: the effect of RD was highly significant [$F(1,128) = 27.220$, $p < .001$, $Eta^2 = .181$], whereas the ADHD was moderately significant [$F(1,128) = 4.155$, $p < .05$, $Eta^2 = .035$].

It should be noted that children with ADHD+RD recalled fewer words than children with ADHD-only [$F(1,53) = 7.100$, $p < .02$, $Eta^2 = .122$]. However, this difference was not due to the difficulty to apply memory strategies because children with ADHD-only were significantly poorer than children with ADHD+RD in recalling words in clusters across the three lists [$F(1,53) = 4.304$, $p < .05$, $Eta^2 = .078$]. More critically, a difference between the two groups of ADHD was found concerning the ability to apply the semantic clustering strategies across the three lists: the

interaction Group by List was significant [$F(1,51) = 4.304$, $p < .05$, $Eta^2 = .078$]. As reported on figure 10/b.1 children with ADHD-only did not show a steep increase in the proportion of words in clusters across the three lists, whereas children with ADHD+RD and RD-only performed like Controls.

Figure 10/b.1

Proportion of words recalled in clusters in the three list of the Strategic Free Recall Task.



A Linear regression analysis (Stepwise Method) was performed in order to understand which variables could predict this performance. The following variables were entered: Inattention and Hyperactivity symptoms according to parents or teacher, IQ, Digit Span (scaled score of the WISC-R), speed of reading (because children were asked to read by themselves the lists of words), speed of object naming (because lexical access could be involved), Memory strategies (increase of words recalled in clusters) and incorrect recall of words (Interferences and Repetitions, because the

memory system could be overloaded by irrelevant items). The only variables that predict the number of words recalled were Inattention according to parents and Digit span $R^2 = 0.416$ [$F(2,67 = 23.135, p < .001$]. The predictive value of Inattention according to parents was $t = 4.372$ ($p < .001$), and the predictive value of Digit span was $t = 3.795$ ($p < .005$). According to these results our hypothesis is that the poor performance in this task is probably due to verbal working memory and attentional deficits.

Finally we were interested to analyse the capacity to control interferences from memory: in particular the amount of Proactive Interference (words recalled but belonging to previous lists), the Repetitions (an item recalled more than once within the same list) and the Extra-list Intrusions (an item recalled but never presented in any list) were analysed.

Three 2 x 2 MANCOVAs (ADHD by RD) were performed on Proactive Interference, Repetitions and Extra-list Intrusions, but no effect was significant. The results of the four groups are reported on table 10/b.2.

Table 10/b.2. Strategic Free Recall Task.

Proactive Interferences, Repetitions, and Extra-list Intrusions

Variables	ADHD-only (N = 38)		RD-only (N = 39)		ADHD+RD (N = 17)		NC (N = 37)	
Proactive Interference	Mean	*S.D.*	*Mean*	*S.D.*	*Mean*	*S.D.*	*Mean*	*S.D.*
List 2	0.48	0.78	0.60	0.76	0.38	0.74	0.55	0.76
List 3	1.30	1.72	1.99	1.69	0.94	1.64	1.13	1.70
Repetitions								
List 1	0.98	1.07	0.51	1.05	0.59	1.02	0.62	1.05
List 2	0.69	1.33	0.66	1.31	0.48	1.26	1.02	1.31
List 3	1.05	1.34	0.49	1.33	1.05	1.29	0.79	1.33
Extra-list Intrusions								
List 1	0.15	0.39	0.23	0.76	0.58	0.63	0.26	0.57
List 2	0.09	0.27	0.22	0.63	0.13	0.34	0.02	0.17
List 3	0.14	0.44	0.65	0.97	0.12	0.34	0.15	0.35

Note. Values are corrected by age.

10/b.4 Discussion

In study 2 a Strategic Free Recall task was administered to four groups of children: Normal Controls, ADHD-only, Reading Disordered (RD-only) and ADHD+RD. The task included three lists of 24 words each, in which 8 of them were fruits, 8 were animals and 8 belonged to other unspecific categories. In the list 1 and in the list 2 the order of the words was not blocked into categories, whereas in the list 3, the order of the words was blocked. Moreover, before the presentation of the list 2 and the list 3, the examiner suggested to the children that they should use a learning strategy (semantic clustering) to improve their recall performance ("If you put together the fruits and the animals, it is more likely that you recall more words"). No suggestion was given on

the presentation of the list 1. Finally, in the list 2 and in the list 3 half of the words had been presented in the list 1 and in the list 2, respectively. The repetition of some words was introduced in order to assess the ability to control the proactive interferences in memory.

Children with RD-only and ADHD+RD were more impaired in this task, considering the Total number of words recalled in the three lists but in particular in List 1 and List 2 where the material was not blocked. Their deficit was due to the presence of RD.

A more complex, but similar, version of this task is the California Verbal Learning Task for Children (Delis et al., 1994): on that task other studies were carried out involving children with ADHD or RD.

Kramer et al (2000) tested 57 children with Dyslexia and found that the dyslexic group learned the list items more slowly, recalled fewer words on the last learning trial and the delayed trials, and performed less well on the recognition condition. The authors interpreted their results in terms of less efficient rehearsal and encoding mechanisms, resulting in deficient encoding of new information, but normal retention and retrieval, because there was no interaction Group by period of recall. Thus, although children with dyslexia learnt fewer words than controls they were able as controls to retrieve the material after a long delay (20 minutes). Moreover, dyslexics were not vulnerable to proactive interferences, as we found in our study.

The literature on the analysis of episodic memory performance of children with ADHD is more controversial, mostly analysing the studies which proposed the retrieval of words presented in lists.

In our study, a deeper analysis of the performance of children with ADHD was carried out, and it gave us some explanations about the controversies and the reasons because children with ADHD do not show any short-term memory deficit but they are unable to give satisfactory performance at school when they are required to study. The focus of this study was the analysis of the use of learning strategies and the ability to inhibit interference from long term memory.

Our results clearly showed that the presence of RD determines more difficulties to recall words across the three lists, whereas the effect of ADHD was only significant in the list 3, where the

words were presented in a blocked order. More specifically the effect of ADHD was found subtracting the number of words recalled in clusters minus the number of words recalled not in clusters. This result showed that children with ADHD do not have a generalized impairment in the recall but in particular in the organization of the material that must be recalled. The consequences of the difficulties to organize the material to recall could not be particularly evident in a free recall task, but in school activities, in particular in the study of subjects, such History, Geography or Science where the information must be organized.

Our results partly confirmed those published by Cornoldi et al (1999) who demonstrated that children with ADHD know many learning strategies, as they indicated on a metacognitive questionnaire, but they were unable to efficiently apply these strategies although they indicated that they should learn using semantic clusters.

In our study, metacognitive knowledge of the learning strategies has not been assessed but, in lists 2 and 3, the examiner told children to organize the words in semantic clusters in order to improve their recall. This manipulation was introduced to assess if the indication of a useful learning strategy (semantic clustering) may help the recall of all children of a particular group. As Cornoldi et al (1999) found, the simple proposal of the use of a learning strategy is not a powerful strategy to change their performance.

In addition, Cornoldi et al (1999) showed that children with ADHD produced more Proactive Interference errors, and they concluded that children with ADHD also have problem of inhibiting from their memory items that were no longer important for the current task. In our study, ADHD children did not produce more Proactive Interference errors, Intrusions or Repetitions than Controls, therefore we cannot confirm that children with ADHD have difficulties in remembering only the correct items and rejecting the wrong ones, as supposed by Cornoldi et al (1999). It is necessary to underline some differences between our study and that published by Cornoldi et al. (1999): we used three lists of 24 words, organized in two categories, whereas Cornoldi et al (1999) had four matrices of 16 pictures organized in four semantic categories; therefore the possibility to confound the items

presented in previous lists was higher in the study published by Cornoldi et al (1999) because children were forced to use more semantic categories of stimuli than they did in our study.

A similar version of our task is the California Verbal Learning Test for Children – CVLT-C (Delis, Kramer, Kaplan & Omer, 1994). Cutting, Koth, Mahone and Denckla (2003) presented ADHD children with this test and they found that ADHD children were particularly impaired in delayed recall, whereas they did not differ from controls on the index of semantic clustering. Compared to our Strategic Free Recall task, in the CVLT-C the examiner read the five word lists that the children has to learn and recall the words immediately or after a delay (short and long). In our task the children have 90 seconds to read the words silently; thus they have more possibilities to organize the words in semantic clusters. In our opinion the CVLT-C does not allow the subjects to easily produce semantic clusters; for this reason the CVLT-C is not sufficiently sensitive task to assess memory organization in children.

From our results, since the group of children with ADHD did not show adequately to organize the information in memory, we postulate that the encoding process, and partly the retrieval one, is negatively affected by this deficit. This difficulty could lead to poorer performance in delayed recall as suggested by Cutting et al (2003). These consequences became clearer at school where children with ADHD show many difficulties in studying and retaining for a long period complex texts that must be organized in long term memory.

From a neuropsychological point of view, many authors (Gershberg & Shimamura, 1995; Incisa della Rocchetta & Milner, 1993; Moscovitch, 1992; Stuss et al., 1994) demonstrated that a poor performance on a task that requires the organization of information in memory could be due to a frontal dysfunction. These results support the hypothesis that only children with ADHD show a deficit of organization of information in memory, whereas children with RD did not show a specific impairment of organization but in the recall of words. The RD deficit, could be analysed comparing our results to what Kramer et al (2000) found: it is interesting to note that our dyslexic children showed a deficit in the total number of words recalled but, across the lists of words they were able

to organize the material as well as controls, and that they did not recall many words outside the clusters. This result could lead us to suppose that the recall deficiencies found in RD and ADHD would be due to different reasons: the results of children with RD are in line with Kramer et al (2000) who suggested that the deficit of children with RD could be more related to the processing of the words; whereas the ADHD deficit could be more linked to the organization of the material, namely the lists of words. Organization is possibly thought as an encoding process, it may also be involved in retrieval, therefore it is plausible, from an anatomical point of view, that children with ADHD may suffer of a dysfunction on the dorsolateral prefrontal cortex (in this case the encoding impairment may be localized in the left hemisphere), and children with RD of a deficit in processing words to be memorized.

Appendix 10.1

Strategic Free Recall Test

List 1. Now, I show you some lists of words. I read you first the list then, I give you one minute and half for studying the words. After one minute and half, I'll take back the list and you will try to recall as many words as possible.

List 2. As you have, probably, noticed, in the list, nouns of animals and fruits are included but not in order. Now, I read you the list first, then you'll study the words and after one minute and half you will try to recall as many as possible, as before.

List 3. In the list 3, like in the previous lists, animal and fruits nouns are presented, but now they are ordered in blocks for helping you a better performance. I read you the list, then you will study it and then you'll try to recall as many words as possible.

LIST 1	**LIST 2**	**LIST 3**
Apple	Mandarin	Frog
Dog	Ruler	Rabbit
Book	Fly	Cow
Elephant	Melon	Bee
Pineapple	Candle	Fly
Box	Mouse	Duck
Orange	Pear	Butterfly
Cat	Motorbike	Monkey
Comb	Frog	Plier
Mouse	Eagle	Button
Melon	Pliers	Watch
Ruler	Cherry	Needle
Lemon	Butterfly	Candle
Horse	Toothbrush	Guitar
Toothbrush	Strawberry	Flag
Lion	Lemon	Hammer
Watermelon	Flag	Pear
Ball	Horse	Apricot
Banana	Kiwi	Kiwi
Turtle	Book	Grape
Cup	Watch	Mandarin
Eagle	Dog	Peach
Cherry	Cow	Strawberry
Motorbike	Apple	Plum

Chapter 11

The role of the DRD4 gene on the neuropsychological performance of children with ADHD and RD

11.1 Introduction

During the past decade genetic research on ADHD has aimed at the identification of candidate genes that may be involved in the etiology of ADHD. Genes controlling the dopamine system are obvious choices to investigate for two main reasons: (1) the effective reduction of symptoms of ADHD brought about by pharmacological agents that act primarily on the dopaminergic and noradrenergic systems (Civelli, Bunzow, Grandy, Zhou & Van Tol, 1991); and (2) results from imaging studies of ADHD which implicate brain structures with rich dopamine innervations, such as the fronto-striatal circuitry (e.g. Castellanos, Giedd, Marsh, Hamburger, Vaituzis, Dickstein et al., 1996). The effects of Dopamine genes are therefore under careful examination by many research groups interested in ADHD.

Almost all studies on the DRD4 gene claimed that the 7 repeat allele is the risk factor for ADHD, but a couple of papers (Swanson et al., 2000; Manor, Tyano, Eisenberg, Bachner-Melman, Kotler, & Ebstein, 2002) found that ADHD children without the risk allele (homozygotic for the 2-5 repeat allele) had poorer performance on neuropsychological tasks measuring response speed and the ability to withhold incorrect responses. In order to investigate the role of other genes in ADHD aetiology, Fisher, Francks, McCracken, McGough, Marlow, MacPhie et al. (2002) performed a genome-wide scan: they analysed 126 affected sib pairs and this indicated that it is unlikely that a major gene involved in ADHD aetiology will be found. Qualitative trait maximum LOD scores higher than 1.5 were found on the 5p12, 10q26, 12q23 and 16p13 chromosomes. None of these regions includes DAT1 or DRD4 genes, but only three of the candidate genes (DRD5, 5HTT and CALCYON) coincided with sites of positive linkage found by this screen.

Only three studies combining genetic analysis and the neuropsychological performance of ADHD children have been published to date (Swanson et al., 2000; Manor et al., 2002; Langley et al., 2004). Swanson et al. (2000) compared the performance of 32 ADHD children (13 with the 7 repeat allele and 19 with the 2-5 repeat allele) to that of 21 controls on three Reaction Time tasks (Stroop, Cue-Orientation and Change tasks). Surprisingly, the performance of ADHD children with the risk allele (7 repeat) did not differ significantly from the Controls, but ADHD children without the risk allele were significantly more impaired than Controls on all the three tasks. The authors concluded that the presence of the 7 repeat allele is not a necessary condition for ADHD (more than half of the ADHD children do not have this allele) and also the 7-repeat allele is not able to identify a subtype of ADHD with more severe cognitive impairments. Moreover, it should be noted that no significant difference was found between the two subgroups (with or without 7 repeat) of children with ADHD in the studies carried by Swanson et al. (2000).

Manor et al. (2002) tested 132 ADHD children using the TOVA (Test Of Variables of Attention; Greenberg & Waldman, 1993) and they confirmed that the sub-group with the 2-5 repeat allele performed significantly more poorly than ADHD children with the 6-8 repeat allele, on the number of Commission Errors and the Variability of Reaction Time within subject's performance. However they did not find any significant difference for the number of Omission Errors and Reaction Times of Responses. Adding the neuropsychological results to the higher probability of transmission of this allele within ADHD families, the authors concluded that the true risk allele for ADHD is the 2-5 repeat allele and not the 6-8 repeat.

Langley et al. (2004) tested 133 drug-naive ADHD children who fulfill diagnostic criteria according to DSM-IV or ICD-10, and 40 Control children. They were presented with a neuropsychological battery including a Matching Familiar Figure Test (MFF), a Continuous Performance Test (CPT), a Go/No Go task and a Stop Task. The group of 25 ADHD children with 7-repeat allele made significantly more errors on the MFF and gave significantly faster incorrect responses on the Stop Task than the group of 53 ADHD children without 7-repeat allele. However,

the two groups of ADHD children did not differ on CPT and Go/No Go measures. Moreover, children with 7-repeat allele were more hyperactive during the administration of the tests (their motor activity was measured using an actigraph attached on their wrist; and they showed more symptoms of ADHD. The main limitation of this study is that is not perfectly clear if ADHD children with 7-repeat allele showed more severe impairments because they were also clinically more impaired (more severe symptoms, presence of comorbidities) or they were actually different from ADHD children without 7-repeat allele, from a behavioral and cognitive point of view.

The current study investigate the performance of ADHD children with two different forms of the D4 allele (2-5 repeat vs 6-8 repeat alleles) on a neuropsychological battery in order to find possible differences between these two genotypes of ADHD.

11.2 Method

From thirty-one ADHD-only children (matched for age to Controls) genomic DNA has been extracted, and on these children combined genetic and neuropsychological analysis have been carried out. The subjects were selected according the procedure described in chapter 6. 10 children with ADHD-only presented the 7-repeat allele (4 have both ADHD and RD) and 21 children with ADHD-only did not present the 7-repeat allele.

Genomic DNA was extracted with a standard SDS/ Proteinase K method (Current Protocols in Human Genetics, Unit 9.7) from a 3 ml venous blood sample. Each subject was genotyped following published procedures for DRD4 48bp repeat (Macciardi et al., 1994) and the DAT1 40bp repeat polymorphisms (Vandenberg et al., 1992).

In this chapter the main measures of study 2 have been considered for the combined analysis (genetics and neuropsychology): Junior Brixton (Total Errors), Junior Hayling (Total Score and RTs of correct responses minus RTs of incorrect responses of Section B), Verbal Fluency (Letter and Semantic), Number Stroop Task (Errors and RTs in Counting Digits condition minus RTs in Counting Stars condition), SART (MRT, Commissions, Omissions), Vigilance Task (MRT and

Omissions), Free Recall Task (Total words recalled and Words in clusters in list 3 minus Words in clusters in list 1), TEA-Ch subtests in scaled scores (Sky Search, Score!, Sky Search DT, Walk Don't Walk, Opposite Worlds).

11.2.1 Procedure

Participants were tested individually in three sessions lasting 45 minutes each. In the first session, the IQ and Reading tests were administered; and in the second and third sessions the neuropsychological battery was administered, during which the order of the tests was counterbalanced across subjects.

11.3 Results

Sixty-eight children were selected: 37 Normal Controls and 31 with ADHD: age, IQ and ADHD symptoms are presented on table 11.1. Controls children were significantly older than the group with ADHD, therefore in statistical analysis age values were partialled out.

Table 11.1

Age and cognitive-behaviour characteristics of NC and ADHD. ADHD participants are split into 2 sub-groups: with or without the 7-allele of the D4 gene

Measures	ADHD 7 repeat N = 10		ADHD no 7 repeat N = 21		NC N = 37	
	M	*(SD)*	*M*	*(SD)*	*M*	*(SD)*
Age	9.12	(1.73)	9.33	(1.24)	10.26	(1.60)
IQ	99.50	(9.14)	103.19	(12.06)	102.92	(7.57)
Inattention	15.32	(4.72)	15.97	(4.51)	4.35	(3.39)
Hyperactivity	14.57	(3.56)	16.83	(4.45)	2.91	(2.41)

Note: Inattention and Hyperactivity values are obtained from the means between Parents' and Teachers' score of the DBD.

The neuropsychological performance of the three groups (Controls, ADHD-7 repeat and ADHD-no 7 repeat) are reported on table 11.2.

Table 11.2

Mean and Standard Deviation of the main neuropsychological variables. Normal Controls are compared with the sub-groups with ADHD (with or without the 7-allele of the D4 gene).

Measures	ADHD-only 7 repeat N = 10	ADHD-only no 7 repeat N = 21	NC N = 37
	M *(SD)*	*M* *(SD)*	*M* *(SD)*
Attention			
SART: RTs	693 (71)	**728 (67)**	634 (106)
Vigilance: RTs	770 (150)	**810 (133)**	690 (120)
SART : SD of RTs	**208 (77)**	**215 (43)**	157 (49)
SART: Omissions	**3.54 (6.28)**	**3.66 (7.55)**	0.27 (0.46)
Vigilance: Omissions	0.27 (0.48)	**0.98 (1.26)**	0.19 (0.39)
Sky Search	7.39 (2.82)	8.19 (1.44)	9.46 (2.66)
Score!	7.85 (2.75)	**7.44 (2.59)**	10.38 (1.92)
Sky Search DT	8.03 (3.28)	6.88 (3.84)	8.13 (3.15)
Walk don't Walk	5.72 (2.91)	5.94 (3.13)	7.62 (3.66)
Opposite Worlds	9.43 (2.50)	9.69 (2.54)	10.95 (2.00)
Executive Function			
SART: Commissions	6.18 (5.78)	4.34 (2.79)	4.31 (2.90)
Stroop: Errors	2.12 (2.00)	3.05 (3.22)	2.02 (2.19)
Stroop: difference RTs	91 (489)	283 (529)	84 (293)
Free Recall: Words	**26.94 (6.09)**	**27.85 (6.73)**	32.75 (9.81)
Free Recall: Clusters 3 -1	1.92 (2.92)	1.02 (2.84)	2.83 (3.51)
Brixton: Total Errors	11.28 (3.17)	9.95 (4.79)	10.53 (3.37)
Hayling: Score	**4.34 (2.91)**	3.86 (1.58)	2.72 (1.94)
Hayling: RT u-(c+s)	1.70 (3.30)	1.18 (2.01)	0.20 (2.15)

Fluency: Letter	14.45 (4.95)	14.44 (3.46)	14.77 (4.57)
Fluency: Semantic	20.76 (5.17)	18.16 (4.56)	19.51 (4.14)

Note. In **bold** significant difference of performance between clinical groups and controls are reported.

A MANCOVA (age covaried) was performed on the entire neuropsychological battery in order to compare the three groups of children. Significant differences were found on: Total Score of the Junior Hayling [$F(2,67) = 3.384$, $p < .05$, $Eta^2 = .096$]; MRT, Omissions and SD of RTs of the SART [$F(2,67) = 7.821$, $p < .01$, $Eta^2 = .196$], [$F(2, 67) = 3.378$, $p < .05$, $Eta^2 = .101$] and [$F(2, 67) = 12.056$, $p < .001$, $Eta^2 = .196$] respectively; RTs and Omissions of the Vigilance task [$F(2, 67) = 6.184$, $p < .01$, $Eta^2 = .162$] and [$F(2, 67) = 7.159$, $p < .01$, $Eta^2 = .183$] respectively; Total words recalled in the Free Recall Task [$F(2, 67) = 4.533$, $p < .02$, $Eta^2 = .124$]; Score! [$F(2, 67) = 3,408$, $p < .05$, $Eta^2 = .096$].

Post-hoc comparisons revealed that children with ADHD-only and the risk allele (7 repeat) of the DRD4 performed specifically and significantly more poorly than Controls only on the Junior Hayling ($p < .05$). Whereas children with ADHD-only and without the risk allele performed specifically and significantly more poorly than Controls on: MRT of the SART ($p < .01$), MRT ($p < .01$) and Omissions ($p < .01$) of the Vigilance task and on Score! ($p < .05$) of the TEA-Ch. Both sub-groups of ADHD-only performed more poorly than Controls on: SD of RTs ($p < .01$) and Omissions ($p <.01$) of the SART; Total words recalled in the Free Recall Task ($p <.05$).

No differences were found between ADHD with 7 repeat allele and ADHD without 7 repeat allele.

11. 4 Discussion

In this study we investigated the performance of ADHD children with different forms of the D4 allele using tasks similar to those studied by Swanson et al. (2000) and by Manor et al. (2002), from which they drew strong conclusions concerning the genetics of ADHD, and in particular on the role of the D4 gene. However we carried out the investigation with two additional

considerations in mind. The first was that we also examined the role that possession of the 7 repeat allele of the D4 gene plays in other types of tasks which are sensitive to ADHD. Secondly we examined its role in a second type of developmental disorder – Reading Disorder – to assess whether any effect of possession of one or other alleles was specific to its occurrence in ADHD or independent of syndrome.

Swanson et al. (2000) found that RT performance on the Stop task was sensitive to the absence of the 7 repeat allele of the D4 gene: ADHD children without the 7 repeat allele were slower and produced more variable responses. On related type of attentional tasks, namely the TOVA, similar to the Continuous Performance Test, Manor et al. (2002), found that subjects with the 2-5 repeat allele of the D4 gene, corresponding to those children without the 7 repeat allele analyzed in Swanson et al.'s (2000) study, made more commission errors and showed higher variability in RTs of correct responses than ADHD with 7 repeat allele.

We investigated the performance of ADHD children on three tasks (Stroop, SART and Vigilance Task) with properties related to those studied by Swanson et al. (2000) and by Manor et al. (2002). In all three we replicated the surface findings of Swanson et al. (2002), namely the children in the ADHD without 7 repeat allele group are slower than controls on the SART, Vigilance and Stroop Task. Moreover, the ADHD without 7 repeat allele group made more omission errors on the SART and on the Vigilance task and showed higher individual standard deviations on the RT of correct responses on the SART. This set of results partly replicated those obtained by Manor et al. (2002): we found higher variability of responses, but not a higher number of commission errors produced by the ADHD without 7 repeat allele group compared to Normal Controls.

Thus in our study we found that children in the ADHD without 7 repeat allele were more impaired in giving fast responses on all three RT tasks, they gave more variable responses on the SART, made more omission errors on the SART, and on the Vigilance task compared to Controls. However, the ADHD without 7 repeat allele group did not differ significantly from those in the

ADHD with 7 repeat allele group. Manor et al. (2002) found that ADHD children and 2-5 repeat made significantly more commission errors and significantly more variable responses than ADHD children with the 7 repeat; but Swanson et al. (2000) did not find a significant difference between the two ADHD groups on any of their tasks. In our study, we failed to find a significant difference between the two allele subgroups on any of the three tasks. Swanson et al. (2000) explained this failure to properly support the hypothesis in the following fashion: *"This suggests that the 7-repeat allele may identify a subgroup with the behavioral but not the cognitive components of ADHD.... In contrast, for a complex disorder like ADHD, we suggest that the 7-absent subgroup is most certainly nonhomogeneous, and composed of individuals with other genetic abnormalities or nongenetic etiologies. These could include (i) other alterations in the highly variable DRD4 gene itself not analyzed in the current study, (ii) alterations in other relevant genes such as DAT1, and (iii) minimal brain damage (MBD) or dysfunction. We propose that these other etiologies produce both the behavioral abnormalities reflected as symptoms of ADHD and the cognitive abnormalities reflected by longer RTs and SDs..."* (pp. 4757 - 4758).

However in both the study of Swanson et al. (2000) and in ours, the group which showed no significant difference from the controls was the smaller group (usually, roughly only one third of the sample have 7 repeat). Therefore detection of a significant difference from the normal control group would a priori require a larger effect size for the target group. Overall considering this set of evidence there is no statistically solid support for the Swanson et al. (2000) claims of the higher vulnerability of the ADHD without 7 repeat allele group.

Manor et al. (2002), in turn, claimed that children with ADHD with 7 repeat allele is a "protective" condition because they did not show the crucial deficits of ADHD: inhibitory deficits (more commission errors) and inconsistent performance (higher SD of RTs of correct responses). According to our results, the presence of the 7 repeat allele is <u>not</u> a protective factor because the subgroup the ADHD with 7 repeat allele group performed somewhat more poorly on other tasks, such as Junior Hayling, a more complex task (the only test that differentiated the ADHD and RD

groups) tapping more specifically the executive function domain. This was mainly due to the difficulty of children with ADHD to shift semantic set and to produce a word unrelated to the given sentence. Thus, more refined analysis on the Junior Hayling revealed that only the *s-type* responses differentiated the ADHD with 7 repeat from Controls [$F(2,61) = 3.37$, $p < .05$]: when a child produced a semantically related word (*s-type* response).

In summary we found a pattern of results for ADHD children similar to those obtained by Swanson et al. (2000) and by Manor et al. (2001) on the Reaction Time tasks. However, there was no significant difference between ADHD groups with different genotypes on these tasks.

The critical findings of this study, however, are that the claim that the 7 repeat allele is a risk factor for ADHD performance is not corroborated even for reaction time tasks, if one takes into account group size. Indeed the non 7 repeat allele is the risk factor for the Hayling test, which is the main task of those used which differentiated the ADHD group from the RD group and the normal controls.

Chapter 12

Summary of results and conclusions

The present chapter is organized as follow: firstly the comparisons between each clinical groups and normal control on the neuropsychological tasks of the two studies are presented, secondly the main neuropsychological functions (Attention, Inhibition, Memory, Set-shifting, Strategy application) investigated are discussed, thirdly the results obtained from the combination of genetics and neuropsychology are summarized, fourthly a qualitative and quantitative analysis between ADHD-only and ADHD+RD is reported, fifthly general conclusions on the differences between ADHD and RD on Attention and Executive Functions are reported; finally the main neuropsychological theories on ADHD are discussed considering the results obtained in these studies.

12.1 Comparison between each clinical groups and normal controls on the neuropsychological tasks

The key results of the two studies are summarized in tables 12.1 and 12.2, and are organized according to the cognitive functions that presumably the tasks intended to measure: Attention (Energizing responses, Vigilance/Monitoring, Visuo-spatial and Counting), Inhibition, Memory, Set-Shift, Strategy application and Verbal Fluency. In study 1, Attention (Visuo-spatial and Counting) and Strategy application are not considered because there are no variables to assess these cognitive processes. In study 1 a comparison between ADHD and Controls was carried on all key variables and Alpha level was set at 0.05. In study 2, multiple comparisons between each clinical group (ADHD-only, RD-only and ADHD+RD) and Controls, therefore the Alpha level was set at 0.017 (0.05 / 3).

On table 12.1 five cognitive domains were considered to compare ADHD vs Controls: Attention (Energizing responses and Vigilance/Monitoring), Inhibition, Memory, Set-Shift and Verbal Fluency. Attention, in particular Energizing responses, according to the definition reported

in Stuss et al (2005) includes the RT of correct responses on the SART and primarily requires the activation of the Anterior Cingulate Gyrus. Vigilance/Monitoring includes RT of correct responses and Omissions of the Vigilance Task and Omissions of the SART and primarily requires the activation of the Right Prefrontal Cortex. Concerning the variables of Attention higher values mean worse performance, because if a subject is not attending correctly the task, he is slow or omits to response to stimuli.

Inhibition includes the number of Commission errors to the SART and the Errors to the Number Stroop task: in both cases the subjects are not able to withhold an incorrect response.

Memory includes only the number of correct responses to the N-back working memory task: the higher the values, the better the performance.

Set-shift includes the Total score at the Junior Hayling because children have to rapidly change the semantic set given by the sentence and to find out a semantically unrelated word. Moreover, the number of Perseveration at the Junior Brixton is considered a measure of set-shift because subject has to inhibit a previous rule and to change mental set toward another schema.

Verbal fluency is the total number of words produced in the three sets of tasks lasting 1 minute each, in which children have to produce as many words as possible beginning with a given letter.

The significant difference between normal controls and ADHD are reported with stars (the results are drawn from chapter 7, 8 and 10/a, study 1).

Table 12.1

Study 1: Summary of key results and comparisons between ADHD and NC

Measures	ADHD N = 31	NC N = 33
Attention : Energizing Responses		
SART: RTs (msec)	649 (70)**	603 (77)
Attention : Vigilance/Monitoring		
Vigilance: RTs (msec)	683 (142)*	668 (94)
SART: Omissions	4.49 (8.11)***	0.03 (0.49)
Vigilance: Omissions	2.58 (2.37)***	0.60 (1.05)
Inhibition		
Stroop: Counting Errors (0-48)	2.53 (2.43)**	1.09 (1.26)
SART: Commissions	12.48 (6.22)***	5.90 (3.20)
Memory		
N-back: Correct responses (0-20)	9.68 (4.77)***	14.85 (3.90)
Set-shift		
Hayling-B: Total Score	4.10 (2.43) *	2.48 (1.86)
Brixton: Perseverations	5.43 (2.91)*	3.73 (2.11)
Verbal Fluency		
Phonemic (tot. words)	12.79 (4.83)	15.09 (4.80)

Note: * = $p < .05$; ** = $p < .01$; *** = $p < .001$. Standard deviations are reported in brackets. Values are corrected by age.

Inspecting table 12.1 the most significant differences between ADHD and Controls were obtained on the Omissions and Commissions of the SART (detailed results are reported on chapter 8), the Omissions of the Vigilance tasks (see chapter 8) and on the number of correct responses of the N-back task (see chapter 10/a). Other significant differences between children with ADHD and controls were found on the Number Stroop and on the speed of correct responses (median RTs) of

the SART (see chapter 8). Finally, children with ADHD performed more poorly than controls on the Junior Brixton, on the Junior Hayling (see chapter 7) and on the speed of correct responses (median RTs) of the Vigilance task (see chapter 8). The only measure that did not differentiate ADHD from controls was the Verbal Fluency Task (see chapter 7).

On table 12.2 key results of study 2 are reported in order to compare the four groups of children (ADHD-only, RD-only, ADHD+RD, and Controls). On table 12.2 two new areas of investigation are included: Strategy Application and Attention Visuo-spatial and Counting processes. This domain includes Sky search (that is a visual search task, lasting about 2 minutes), Score! (that is a keep counting of sounds tasks, lasting about 10 minutes) and Sky Search Dual Task (that is a combination of the two latter tasks, lasting about 2 minutes).

As far as the Inhibition measures are concerned other variables are included in study 2: Errors of the Number Stroop task, and Walk Don't Walk performance. The Errors of Stroop task were considered a measure of inhibition because if children make this error if they do not inhibit the automatic response (they named the digits instead of counting them). Walk Don't Walk is a measure of Inhibition because low scores are due to the difficult to stop the incorrect response corresponding to the "no-go" signal. Moreover, concerning Memory a different measure was used because in study 2 a Strategic Free Recall task was used instead of the N-back working memory task.

Compared to study 1, in study 2 Set-shift includes also the difference of RTs in the two conditions of the Number Stroop task (Counting stars vs Counting digits). This variable reflects the cognitive cost of the subjects to shift from one type of activity (Counting stars as baseline) to another one (Counting digits as Stroop condition). The performance on the Opposite Worlds is considered a measure of set-shift because is a composite score including the activity of stopping the automatic response (naming the number presented on the card) and of activating the controlled response (saying the contrary of the number presented).

The area Strategy Application includes two variables: one derived from the Junior Hayling (concerning the speed of correct responses) and one from the Strategic Free Recall task (concerning the increase of proportion of words recalled in clusters across the three lists).

Finally, on study 2 two different types of Verbal Fluency tasks were included: Phonemic and Semantic Fluency.

The significant difference between normal controls and clinical groups are reported with stars. Alpha level was set at $p = .017$. The results are drawn from chapter 7, 8 and 10/a, study 2. Values are corrected by age in order to compare the two studies, apart from the results of the TEA-Ch subtest that transformed in scaled scores according to the norms published by Manly et al., 1998).

Table 12.2

Study 2: Summary of key results and comparisons between NC, ADHD-only, RD-only and ADHD+RD

Measures	ADHD-only N = 38	RD-only N = 39	ADHD+RD N = 17	NC N = 37
Attention: Energizing Responses				
SART: RTs	698 (87)**	747 (115)***	751 (166)***	625 (106)
Attention: Vigilance/Monitoring				
Vigilance: RTs	781 (161)**	830 (139)***	801 (111)**	688 (120)
SART: Omissions	2.57 (3.97)*	1.70 (3.90)	3.71 (6.88)**	0.27 (0.46)
Vigilance: Omissions	0.57 (1.13)	0.81 (1.17)*	0.75 (1.00)	0.19 (0.39)
Attention: Visuo-spatial/Counting				
Score!	7.53 (2.67)***	7.42 (2.96)***	8.62 (3.30)	10.38 (1.92)
Sky Search DT	7.82 (4.25)	5.83 (4.05)*	6.00 (4.55)	8.14 (3.15)
Sky Search	7.75 (2.23)*	7.55 (2.71)**	8.00 (2.10)	9.45 (2.66)
Inhibition				
SART: Commissions	5.02 (3.92)	7.71 (3.95)**	6.70 (6.34)*	4.31 (2.90)
Stroop: Errors	2.53 (2.06)	3.27 (2.13)*	4.07 (2.21)**	2.02 (2.19)
Walk don't Walk	5.17 (3.03)**	5.46 (3.02)*	4.50 (3.20)**	7.62 (3.66)
Episodic Memory				
Free Recall: Words	27.81 (6.56)**	23.58 (8.13)***	22.14 (10.32)***	32.75 (9.81)
Set-shift				
Hayling-B: Total Score	3.77 (1.99)	2.64 (1.94)	3.01 (1.96)	2.72 (1.94)
Brixton: Perseverations	4.47 (2.37)	4.00 (2.50)	4.75 (3.50)	3.43 (2.39)
Stroop: difference RTs	224 (484)	-3 (412)	185 (469)	84 (293)
Opposite Worlds	9.08 (2.56)**	7.92 (2.88)***	8.12 (2.78)***	10.95 (2.00)

Strategy application				
Hayling: RT u-(c+s)	1.29 (2.15)*	0.48 (2.23)	1.09 (2.22)	0.14 (2.15)
Free Recall: clusters (p)	0.21 (0.40)*	0.48 (0.38)	0.46 (0.38)	0.40 (0.28)
Verbal Fluency				
Phonemic (tot. words)	14.32 (4.27)	14.16 (5.20)	12.45 (5.32)	14.99 (4.57)
Semantic (tot. words)	19.18 (4.89)	19.33 (4.80)	18.91 (5.02)	19.66 (4.14)

Note: * = $p < .017$; ** = $p < .003$; *** = $p < .001$. Standard deviations are reported in brackets. Values are corrected by age apart from the scores of the TEA-Ch tests that are scaled scores.

Inspecting table 12.2 it is possible to observe that, concerning Energizing Responses there is a significant difference between ADHD-only and Controls. Moreover there were two significant differences concerning Vigilance/Monitoring between ADHD-only and Controls (namely on Vigilance RTs and SART Omissions). The same pattern of results was found for the group with ADHD+RD compared to Controls. Children with RD-only gave significantly poorer performance than Controls on Energizing Attention (RTs of correct responses of the SART), on two measures of Vigilance/Monitoring (RTs and Omissions of the Vigilance task). Results on the SART and the Vigilance task must be interpreted cautiously in particular with respect to children with developmental dyslexia as the tasks require rapid digit naming, therefore a verbal processing. Since it is well known in the literature that children with developmental dyslexia are primarily characterized by a verbal processing deficit (Snowling et al, 2001; Frith et al., 2003) and have difficulty in rapid naming (Shaywitz and Shaywitz, 1991). It is interesting to observe that children with ADHD+RD showed RTs to the SART very similar to the group with RD-only (their slowness could be due to their verbal processing deficit), but they behave like ADHD-only concerning the Omissions measures. That is: ADHD+RD children are slow verbal processor but also they are ADHD in terms of their difficulties to sustain attention over the task.

Concerning performance on the visuo-spatial and counting tasks of Attention it is interesting to note the performance of the group with ADHD+RD was not worse than the performance of the

two groups with a "pure" disorder; in fact on the three measures the group with ADHD+RD was not significantly different from Controls. Actually, this lack of significance could be due to the reduced sample of children with ADHD but it is interesting to note that, in any case, the two disorders did not add up in visuo-spatial and counting tasks of Attention. Children with ADHD-only and RD-only performed significantly poorer than Controls on the Score! and Sky Search tasks, whereas only the group with RD-only was significantly worse than controls on the dual task. Detailed results are reported in chapter 9, further interpretations of these results are discussed in paragraph 12.2.2.

Concerning the inhibitory processes the two groups with developmental dyslexia are the most impaired groups. Whereas the group with ADHD-only showed an impaired performance on Walk Don't Walk task of the TEA-Ch battery (for details, see chapter 9) but not concerning the number of Commission Errors and the Errors to the Number Stroop task (see chapter 8). Further interpretations of these results are discussed in paragraph 12.2.3.

The performance on the Strategic Free Recall task differentiated the three clinical groups from the Controls; although, concerning the number of words recalled, the two groups with RD performed more poorly than the group with ADHD-only (detailed results are reported in chapter 10/b). Further interpretations of these results are discussed in paragraph 12.2.4.

Three measures of the entire battery assessed the set-shifting skills: Total Score of the Junior Hayling, Perseveration of the Junior Brixton (see chapter 7) RTs of the Stroop effect (see chapter 8) and Opposite Worlds (see chapter 9). Only Opposite Worlds differentiated the four groups. Further interpretations of these results are discussed in paragraph 12.2.5.

Concerning the ability to apply a strategy to achieve a goal two variables were analyzed: the speed of giving correct response to the Junior Hayling (reflecting the use of a strategy, described in chapter 7) and the increase of proportions of words recalled in clusters across the three lists of the Strategic Free Recall Task (see chapter 10/b for details). In this cognitive domain only the group of children with ADHD-only performed significantly worse than the controls. Further interpretations of these results are discussed in paragraph 12.2.6.

Finally the two types of Verbal Fluency tasks (Phonemic and Semantic) did not differentiate the four groups (see chapter 7 for details). Further interpretations of these results are discussed in paragraph 12.2.7.

12.2 Main results of the cognitive neuropsychological functions

12.2.1 Energizing Responses

Inspecting table 12.2 we observe that the three clinical groups performed significantly poorer than controls on the Energizing Responses measures. Actually it is necessary to analyze more in detail the result in order to draw some conclusions concerning the attention functioning of children with ADHD and/or RD.

As reported in chapter 8, there are some differences between the results obtained in study 1 and in study 2. All groups, included controls, were slower in responding to the targets on the SART, in study 2 compared to study 1. This difference was probably due to the technical differences between the two versions of the tasks, because in study 1 the experiment recorded the responses within 1000 msec, whereas in study 2 the experiment was modified and the responses were recorded till 1500 msec.

Concerning the speed of responses to the targets (digits) on the SART in study 2, it has been observed, as reported in chapter 8, that only the RD effect was significant, although the ADHD effect approached to significance. The RD effect could be interpreted as that it is a slower processing of digits that causes their impairments in the two attention tasks (Fawcett & Nicholson, 1996). The combination of the two disorders (ADHD and RD) did not cause an additive effect, therefore the group of children with ADHD+RD are not just the summation of the two disorders (at least concerning the Energizing responses processes).

Moreover, in study 2, we have analysed the effect of the rate of the stimuli (1.5 sec vs 2.5 sec) on the RTs of the correct responses to the SART. Comparing only children with ADHD to Controls, an interaction ADHD by Rate was found to be significant, because children with ADHD

became slower than controls when the presentation rate of the stimuli was slower. This result may supports the theory proposed by Van der Meere (1996) on the State Regulation deficit in children with ADHD: probably they present an attention deficit only when the rate of the stimuli is slow, but their performance is normalized when the rate is faster. After this analysis the RD condition was included into the analysis and the interaction ADHD by Rate on the RTs data of the SART and Vigilance task was no longer significant; however the interaction RD by Rate was statistically significant, because children with RD became slower to respond to digits when the presentation rate of the stimuli was slow (2.5 sec), therefore contrary to the predictions by Van der Meere (1996) the rate of the stimuli does not affect specifically only children with ADHD, but, at least using a rapid digits naming task, also children with RD. Moreover, we expected that children with RD would become less accurate when the presentation rate of the stimuli speed up, because they have problem to rapidly access to the verbal and written information (such as digits on a screen). Contrary to our predictions, children with RD, in the faster condition, speed up their response and they were not less accurate than in the slower condition.

Children with ADHD+RD were significantly different from the other three groups because they did not slow down across the two blocks (first half and second half of each session), whereas ADHD-only, RD-only and Controls slowed down across the two blocks. This result was already obtained in study 1 where the group of ADHD were able to maintain the same response speed across the task but they produced an higher number of comm

seconds). Therefore it is possible that the small manipulation of the experimental condition was not able to specifically test the core deficit of ADHD (activation mediated by external factors) but one of the main deficits of RD, namely rapid process of verbal stimuli. Further studies must clarify if this effect could be to the material proposed in this study (digits to name) and if different rates (e.g. an ISI set at 4 sec) could affect differently these groups of children.

12.2.2. Attention: Vigilance/Monitoring

Concerning the Vigilance/Monitoring measures the results obtained on the RTs of correct responses to the Vigilance task are very similar to those obtained on the RTs of the SART. Moreover, other differences between ADHD and RD children concern the capacity to respond to all targets: children with ADHD made more Omission errors in the SART than in the Vigilance task (see chapter 8, study 2). In order to propose plausible interpretations of the results concerning the number of omission errors in the SART produced by children with ADHD, it is necessary to underline that the SART required to name all but one of nine digits, therefore if the children did not respond to a digits it was not for a deficit in detecting the target, as it was in the Vigilance task (where the children had to name only one out of nine targets). On the SART, ADHD children deliberately did not give a response, since it was clear that they had to respond to all targets. A plausible interpretation is that children with ADHD were not enough motivated to the task and in certain moments of the task administration they did not perform it. If this was the case, an higher number of consecutive omissions must be observed. Data analysis run on the number of consecutive omission errors, did not show any significant difference between ADHD and other groups. Therefore an interpretation in terms of motivation does not hold up. Another plausible interpretation is that children with ADHD were not able to sustain the effort to respond to all targets and sometimes "decided" to refrain their responses (not consecutively). From the observation of their behavior, it seemed that children with ADHD needed some "breaks" during the task performance. This interpretation could be in line with the cognitive-energetic model proposed by Sergeant et al.

(1999) according to which the effort control is one of the key impairments in ADHD. According to other neuropsychological models (e.g. Swanson et al., 1998) it is possible to argue that children with ADHD are constantly less cognitively activated and they present a difficult to self-regulate their attention, for their deficits in the Right Prefrontal Lobe (Stuss et al., 2005). These interpretations are two different ways to underline the same deficit of vigilance and self-regulation of attention, for a problem of endogenous effort control.

12.2.3 Visuo-spatial and counting tasks

In addition to the SART and the Vigilance Task, three sub-tests of the TEA-Ch are discussed here because they require attentional processes: Sky Search, Sky Search DT and Score! The other subtests: Walk Don't Walk and Opposite Worlds will be discussed in the paragraph concerning Inhibition because they have important inhibitory components.

As far as the TEA-Ch battery, in general, is concerned the presence of an RD was the key factor in order to understand the attentional performance of the children tested in the study, as reported on paragraph 9.4. Their performance was significantly poorer, compared to controls on the visual search task (Sky Search), on the counting sound tasks (Score) and on the combination of both (Sky Search DT). In particular, on the dual task their performance was particularly poor compared to controls, this could be a further support to the hypothesis proposed above that their problem of automaticity, rather than lack of attentional resources, may have played a role in determining their performance.

Analysing more carefully the three tests included into this section it is necessary to note that the effect of ADHD was never significant. Only on Sky Search DT the effect of RD was significant, and the interaction ADHD by RD was significant on both Sky Search and Score. The two interactions were caused by the absence of additity in the group with ADHD+RD, compared to ADHD-only and RD-only.

The strong similarities between the behavior of children with ADHD-only and RD-only on Sky Search and on Score! is really surprising because the two tasks loaded on different factors according to the analysis performed by Manly et al (2001) (Sky Search is a task of selective attention; and Score a task of sustained attention). The execution of Sky Search requires good visual search skill, and also good strategy to rapidly detect the targets, whereas Score! requires the capacity to avoid distractions, to update the cognitive system and to count sounds automatically. It is possible that different reasons may play a role in determining the impaired performance of the two clinical group (ADHD-only and RD-only): possibly children with ADHD-only children have problem in maintain their energizing attention on the task (Sergeant et al., 1999) whereas children with RD-only may be impaired for their phonological working memory (see Vellutino et al., 2001) and automatic counting skills (Nicholson & Fawcett, 1999). On the Sky Search DT a RD effect was significant and in this case children with ADHD-only were not impaired. The normal performance of children with ADHD-only may be due to the fact that during the execution of the dual task they were more activated and stimulated to perform better than on the other tasks. This interpretation fits with the proposal of the energizing attentional deficit in children with ADHD proposed in chapter 8 and by Sergeant and colleagues (1999). This interpretation fits also with the observation of the children during the execution of the task, because when they were involved in two tasks they performed better than the two single tasks.

12.2.4 Inhibition

In order to give a summary of the ability to withhold responses four measures of the neuropsychological battery were considered: Commission errors of the SART, Errors on the Number Stroop task, and Walk Don't Walk of the TEA-Ch battery (Manly et al., 2001).

As far as Commission errors of the SART are concerned, in study 1 ADHD children performed significantly poorer than controls, but this significant difference was not replicated in study 2. Comparing the two studies, normal controls made a similar number of errors, keeping into

account that in study 2 the targets were 4/5 of study 1. However, in study 2, children with ADHD reduced the number of commissions and the difference between ADHD and controls was no longer significant. Moreover, the two studies differed for three reasons: 1) the composition of the ADHD sample (in study 1 ADHD children were younger than in study 2); 2) the presence of children with comorbidity (ADHD+RD) in study 2; 3) in study 1 the presentation rate of the stimuli of the SART were faster than in study 2. As reported on figure 8.12, in study 2 younger children with ADHD made more commission errors and they were a bit more inaccurate in the fast than in the slow condition. The difference between the two conditions was not significant, but it is possible that a very fast condition (1 sec as in study 1), could have induced an higher number of commission errors, in particular by younger ADHD children.

In study 2 the presence of RD, not ADHD, was significant. Therefore, as already underlined in paragraph 8.3.5, we postulated that the deficits of automatic decoding of digits caused the impairment on the SART shown by children, as already demonstrated by Moore and Andrade (2001). What it would be interesting to analyse in future researches is a comparison between ADHD and RD on a task similar to the SART without presenting digits or letters, but presenting no-verbal stimuli, such as geometric shapes (no more than 3 types in order to avoid memory overload) and to contrast their ability to inhibit vocal or motor responses.

Another RD effect on a measure of inhibition was found concerning errors of the Number Stroop task: in this case RD children named more frequently the digits, that appeared on the screen, instead of counting them. Compared to study 1, in study 2 the group of children with ADHD made a similar number of errors due to the Stroop effect (compare table 12.1 and 12.2) but controls made almost double errors in study 2 than in study 1, and for this reason (poorer performance of the controls) the ADHD effect in study 2 was not significant. In this case the reasons of this lack of ADHD effect in study 2 was due to at least two reasons: 1) in study 1 the RD condition was not kept into account, therefore it is possible that the poorer performance of children with ADHD in study 1 was due to the presence of children with RD, that, in study 2, was the critical factor to

induce errors for the Stroop effect; 2) in study 2 a Naming digit condition was included between the Counting stars and Counting digits conditions: the request of naming digits was included in order to reduce the learning effect of counting stars (the children learnt how many items were presented on the screen without counting them but because they recognize the visual configuration). The Naming digits condition may have induced an higher number of Stroop errors in the Counting digits condition because children had just finished to name digits and immediately afterwards they were requested to inhibit the automatic response that was trained, and they had to produced an alternative response (counting digits).

A further measure of Inhibition was obtained from the Walk Don't Walk (TEA-Ch) number of correct trials: in this case the effects of both ADHD and RD were found to be significant. Walk Don't Walk assessed the abilities of the children to follow rapid sounds and to control motor manual responses, therefore an error could be due to a failure to follow the rhythm of the sounds or to a failure to stop an incorrect response. Given the standard instructions of the task, it was not possible to differentiate these two types of errors (following the rhythm of the sounds, stopping incorrect responses) therefore it is not possible to interpret the reasons of the poor performance of children with RD or ADHD. It could be very interesting to test if children are impaired in Walk Don't Walk because of their difficulties in controlling motor responses or in following the rhythm of rapid sounds analysing, in future researches, the type of errors.

Among the description of the inhibitory mechanisms, Nigg (2001) proposed a differentiation between Effortful and Automatic Inhibition. Four types of Effortful Inhibition have been described: Interference Controls (usually assessed via Stroop Tasks), Cognitive Inhibition (control of non-pertinent information to protect Working Memory or Attention), Behavioral Inhibition (for suppressing prepotent responses), and Oculomotor Inhibition (effortful control of reflexive saccade). Following the model proposed by Nigg (2001) on different types of Inhibitory processes, it was found that children with RD are impaired in controlling interference (Number Stroop and Walk Don't Walk), whereas children with ADHD were impaired only in the domain of behavioral

inhibition (Walk Don't Walk) if motor responses are required. However, it is necessary to underline that the impaired performances of children with RD involved always rapid processing of digits (Number Stroop, SART and Opposite Worlds) therefore it is not possible to generalize and conclude for the presence of an inhibitory deficit in children with RD, because children with RD are primarily slower processors of verbal material, therefore their difficulties to withhold incorrect responses when rapid naming of digits is required could be due to their deficit in the automatic recognition of the stimuli.

12.2.5 Memory

In order to assess the memory functioning of children with ADHD and/or RD two different tasks were proposed: the first one was an N-back task (to assess Working Memory) and the second one was a Strategic Free Recall Task (to assess Episodic Memory and the use of Memory Strategies) composed of three lists containing 24 words each, partly belonging to categories (Animals and Fruits), partly not categorizable.

The results obtained in study 1 were extremely clear: children with ADHD were impaired in the N-back task even after partialling out the effect of attending the stimuli at 0-back level (attentional factor), as reported in paragraph 10/a.3.

In study 2, considering the number of words recalled in the Strategic Free Recall Task, an effect of ADHD was found to be significant, but the effect of RD was even more significant (paragraph 10/b.3). Actually it is not surprising that children with RD are impaired in a free recall task as repetitively demonstrated by other studies (for a review, Vellutino et al., 2004).

In summary, Memory is one of the most pronounced area of impairment in ADHD. This result was found by the administration of two different paradigms (N-back and Strategic Free Recall Task) which showed that the impairments of children with ADHD were not due to confounding factors associated with the tasks, such as attention or phonological working memory impairments.

12.2.6 Set-shift

A further measure of Executive Functions is Set-Shift, that is the capacity to apply with flexibility new schema in order to achieve a goal. Two types of set shift have been proposed (Downes et al., 1989): intra-dimensional shifts (IDS), which involve the transfer of a rule within the same stimulus dimension (e.g. choosing circles instead of squares), and extra-dimensional shifts (EDS), which require a transfer of attention across different stimulus dimensions (e.g. choosing on the basis of colour rather than the previous category of shape). In essence, EDS shifting is the core component of the WCST, and is the basis for the achievement of novel sorting categories. IDS is a more basic element of the WCST and is related to the ability of the subject to be aware of the conceptual category within which they are responding. A successful IDS shift requires a generalisation of learning or the ability to 'learn set'.

Four measures has been considered as belonging to the construct of Set-Shift: Total score of Section B of the Junior Hayling, the total number of Perseverations of the Junior Brixton, the difference between MRT of the Counting Stars and Counting Digits of the Number Stroop and performance on the Opposite Worlds test. Following the distinction of EDS and IDS, the Score on Section B of the Junior Hayling is considered an Extra-Dimensional Shift since the subjects have to completely change the semantic domain of the sentence. The Perseveration on the Junior Brixton is an index of a difficulty in Intra-Dimensional Shift since the children have to be aware of the rule of the turtle movement. The RT of the Stroop effect is an EDS because the subjects have to count the digits instead of the stars. The performance on the Opposite Worlds is considered a measure of EDS because subjects have to name a different digits respect to what is reading on the cards.

It is necessary to be precise that the performance of the Number Stroop task was included into two different cognitive domains: the number of errors refers to Inhibition, because the variables refers to the failure to stop an incorrect, although automatic response; whereas the RTs of the Stroop effect (the difference of RTs in the two counting conditions: neutral stimuli and digits) reflects the capacity to control interfering stimuli.

Concerning the Junior Hayling, in study 1 an effect of ADHD was found to be significant (paragraph 7.2.3.b), whereas in study 2, a trend of significance ($p < .07$) was found between ADHD-only and Controls but not between ADHD+RD and Controls (paragraph 7.3.4.b). Actually, if all children with ADHD were contrasted to controls, in study 2, the ADHD effect showed a trend of significance ($p < .06$). This partial lack of replication was due to the better performance of the older ADHD in study 2 than in study 1, however the difference between the results reported on tables 7.2 and 7.5 are small. Moreover, if larger samples were compared, Controls vs ADHD, combining the two studies, the ADHD effect was highly significant ($p < .001$), as reported in paragraph 7.4.

A second measure of Set-Shift is the number of Perseverative errors of the Junior Brixton. Again, in study 1 an effect of ADHD was found to be significant (paragraph 7.2.3.a), but in study 2, concerning the effect of ADHD, only a strong trend of significance ($p < .07$) was found (paragraph 7.3.4.a). The explanations of the lack of complete replication between the two studies on the Junior Brixton have been already discussed in paragraphs 7.3 and 7.4, and concerned the different samples between the two studies (in study 2 the group of children aged 7-8 were older than in study 1, and since the Junior Brixton is highly sensitive to age effect, we concluded that the Junior Brixton is appropriate for younger ADHD and for ADHD+RD children).

A third measure of Set-Shift is the difference of RTs in the Counting Stars and Counting Digits conditions of the Number Stroop because children in the latter condition have both to inhibit an automatic response (naming digits) and to activate a secondary, not automatic response (counting digits), therefore the difference of RTs between the two conditions represent the "cognitive cost" to implement this operation. Related to this variable only a significant ADHD trend of significance ($p < .07$) (paragraph 8.3.3.c), but the most pronounced difference was between RD-only and ADHD-only ($p = .035$), probably because children did not absolutely slow down counting digits instead of neutral stimuli (because they did not automatically process the numbers), and because children with ADHD-only may have a mild set-shifting deficit, not observed in the Number Stroop Task.

The fourth measure of Inhibition was obtained from the "Opposite-worlds" subtest of the TEA-Ch (the variable refers to the time to name opposite numbers): in this case children were required to inhibit responses corresponding to a series of digits presented in a row on a card, and asked to name a different label ("1" instead of "2", "2" instead of "1"). Consistently with previous results on the Number Stroop task, the effect of RD was significant also in this case, as presented in paragraph 9.4.3. Moreover, an interaction ADHD by RD was found to be significant because children with RD-only represented the slowest group. Actually a more reliable measure of set-shift derived from the Opposite Worlds test is the difference between the two conditions (Opposite Worlds – Same Worlds) in this case neither the ADHD nor the RD effects were significant, therefore this tasks is highly sensitive to rapid naming digits and there is doubt the validity of this measures to test the functioning of Executive Attention.

In summary, as far as Set-Shifting is concerned, the RD effect is not significant, and this is the only cognitive process, so far analysed, in which the ADHD effect show a trend of significance ($p < .07$). We suppose that specific manipulations of the tasks (Junior Brixton, Junior Hayling and Number Stroop) would help us to find more clearly ADHD effects, adding some more requests of set-shifting processes, because this could be one of most critical impairment of children with ADHD.

From a neuropsychological point of view different authors (Dias et al., 1996; Stuss et al., 2000) proposed that the dorsolateral prefrontal cortex could be the anatomical structure mainly involved in the execution of set-shift, in particular related to Extra-Dimension, activities. Moreover, also according to the Posner and Petersen (1990) model of the three attentional networks the capacity to shift from one of cognitive process to another one, could be implemented by the activation of the anterior cingulate gyrus. Moreover, according to Swanson et al., (1998) the network involved in Executive Attention is one of the impaired cognitive domains in children with ADHD, therefore other studies on the functioning of the anterior cingulate gyrus are needed in order to understand if this structure could be involved in the aetiology of ADHD.

12.2.6 Strategy application

The analysis of the application of strategies - for achieving a goal and for giving good performance - was run considering two measures: the type and the speed of strategic responses on the Junior Hayling and the ability to use semantic clusters across the Free Recall task, from list 1 to list 3. On the Junior Hayling, *ur, ul* and *url* type responses were considered strategic because subjects used the objects in the room (*ur*) or the previous sentences (*ul*) or both (*url*) to produce a word that was semantically unrelated to the sentence. On the other hand, when subjects gave words without using these strategies, the responses were coded as *u*-responses. The variable [(*ur* + *ul* + *url)* – *u*], specifically created, represents a behavior of each subject to give responses using these particular strategies. Considering this variable on study 1 a significant ADHD effect was found to be significant ($p < .05$) (paragraph 7.2.3.b), but in study 2 this effect was not replicated (paragraph 7.3.4.b). Therefore this means that this variable [(*ur* + *ul* + *url)* – *u response*] was not particularly sensitive to ADHD for the reasons already discussed in paragraph 7.4 (characteristics of the two samples). However, a more sensitive measure of the use of strategies was the speed of giving correct and strategic responses: in this case, in study 2 (in study 1 this variable was not collected) the effect of ADHD was significant ($p < .05$) as reported in paragraph 7.3.4.b.

Therefore it is likely that analysing only the type of strategic responses was not possible to detect minor difference in the use of strategies between groups. For this reason the speed of the responses was analyzed in order to understand if the subject were using or not a strategy. For this purpose the RTs of u (correct) responses minus RT of c or s (incorrect) responses was calculated. For this variable the effect of ADHD is significant, perhaps because the variable is more sensitive to small differences between groups.

Finally, considering the ability of the children to produce semantic clusters in order to recall words in the Strategic Free Recall Task, an ADHD effect was found in the last list on the difference between the number of words recalled in clusters and the number of words recalled not in clusters

(paragraph 10/b.3), because Controls and children with RD-only recalled more words in clusters over words not in clusters, but this was not the case for children with ADHD (ADHD-only, ADHD+RD). Even more interestingly, the group with ADHD-only was the unique group which differed from normal controls ($p <. 05$) on the variable which assessed the increase proportion of words in clusters on the total words, from list 1 to list 3. From this analysis, it emerged that children with ADHD-only, were not able, compared with normal controls and children with RD, to apply the strategy of using semantic clusters in order to recall words in a memory task.

As observed in the paragraph on Set-shift, also in the use of strategy, children with RD were absolutely unimpaired, whereas children with ADHD, in particularly children with ADHD-only showed poorer performance, although the differences from normal controls were not so large, therefore, it could be interesting in future researches to analyse more deeply this area - the application of strategies - in order to clarify the main neuropsychological deficits of ADHD and perhaps finding clearer differences between ADHD-only and ADHD+RD.

12.3 On the development of Attention and Executive Functions

Following the table 12.2 about the cognitive functions assessed through this neuropsychological battery some interesting results have been found on the typical development of attention and executive functions. In order to draw some preliminary interpretations, three comparable groups of control children were derived: 7-8 years, 9-10 years and 11-12 years. The performance of the control children, divided into age groups, is reported on table 12.3. In the right coloumn, the pairwaise comparisons were reported, only if the effect of age group was statistically significant.

Table 12.3

Measures	7-8 yrs (N = 9)[a]	9-10 yrs (N=13)[b]	11-12 yrs (N=15)[c]	Age effect F(2,36)	Pairwise comparisons
Attention: Energizing Responses					
SART: RTs	693 (111)	605 (83)	579 (86)	4.44*	a < b,c
Attention : Vigilance/Monitoring					
Vigilance: RTs	762 (177)	704 (63)	610 (87)	5.18*	a,b < c
SART: Omissions	0.11 (0.33)	0.31 (0.71)	0.00	1.49	
Vigilance: Omissions	0.34 (0.60)	0.13 (0.42)	0.00	2.04	
Inhibition					
SART: Commissions	6.11 (3.33)	4.33 (2.74)	2.21 (1.48)	6.88**	a,b < c
Stroop: Errors	2.57 (2.15)	1.90 (0.88)	1.29 (1.32)	1.94	
Episodic Memory					
Free Recall: Words	22.78 (7.08)	35.25 (5.12)	39.07 (9.75)	12.53***	a < b,c
Set-shift					
Hayling-B: Total Score	2.56 (1.59)	3.00 (2.16)	2.87 (1.68)	0.16	
Brixton: Perseverations	4.86 (2.03)	3.38 (1.66)	2.40 (1.88)	4.34*	a < c
Stroop: difference RTs	182 (228)	194 (283)	-62 (287)	3.22	b < c
Strategy application					
Hayling: RT u-(c+s)	-1.16 (2.54)	0.49 (1.89)	0.59 (1.44)	2.49	a < c
Free Recall: clusters (p)	0.48 (0.26)	0.43 (0.33)	0.28 (0.24)	1.73	
Verbal Fluency					
Phonemic (tot. words)	13.67 (3.57)	14.92 (4.05)	17.00 (5.03)	1.78	
Semantic (tot. words)	17.11 (4.01)	19.54 (3.26)	22.73 (3.61)	7.27**	a,b < c

Legend: * p < .05; ** p < .01; *** p < .001. Pairwise comparisons were significant at Alpha = 0.05.

On all measures of attention or executive functions at least one measure, derived from the neuropsychological battery, revealed that in that age window of 7-12 years many aspects of attention and execution functions are still developing. As reported on table 12.3, concerning Energizing attention and the speed of response on the Vigilance task, there were significant difference between age groups, however, for the SART the ceiling effect was found in children aged 9-10 yrs, whereas no significant improvement of the speed of reponses was found between children aged 9-10 and childen aged 11-12. This means that the SART is sensitive from 7 to 10 years, whereas the Vigilance task is sensitive from 9 to 12 years, it seems that the capacity to speed up the responses across ages is different accoring to the specific request of the task: naming almost all stimuli or very few targets. In other words, the energizing attention develops earlier than vigilance and monitoring aspects of attention. In the literature, very few researches were interested to study in details the development of different aspects of sustained attention: only McKay et al (1994) and Rebok et al (1997) showed that sustained attention develops in children from 7 to 16 years using CPT paradigms and considering the speed of responses.

The confirmation that RT of the SART and of the Vigilance requires different cognitive process come from the results of the controls who showed that only older children (11-12 years) performed significantly better than children aged 8-12 yrs.

As far as the Inhibitory processes are concerned children aged 7-8 and 9-10 performed similarly but they made significantly more errors than children aged 11-12 yrs.

Considering the total number of words recalled in the Strategic memory task the age effect was significant and presents a linear trend. Whereas on the Set-shift domain the number of perseverative errors produced on the Junior Brixton showed a linear and significant age effect. Interestingly, on the difference of RTs of the Number Stroop the older group were even faster in counting numbers than counting stars, whereas the other two age groups were slower in the conflicting condition. The fast responses in the conflicting condition of the older children were due to a process of gradual automatization, since the baseline condition was presented before the Stroop

conflicting condition. This means that the experimental manipulation of the Number Stroop was not effective in children aged 11 years onwards.

Among the measures of the strategy application only the speed of strategic responses differentiate the younger group from the older group, therefore this measure was not particularly sensitive to the development because the intermediate group was not different from the younger and the older.

Finally, on the Verbal Fluency tasks only the Semantic Fluency task showed a linear age effect, probably due to the increase of the geneal knowledge, whereas the Letter Fluency task did not show an age effect. The different developmental trend between Letter and Semantic Fluency task confirmed previous studies (e.g. Riva et al., 2000) which showed that the increase of word production is significant only comparing children aged 5 to children aged 11, therefore in age range of the current study the letter fluency tasks probably has reached a plateau. On the contrary, on the semantic fluency task the improvement of the performance due to the development starts later and the difference between age groups is significant between 8 years and 10 years (Riva et al., 2000).

12.4 Have Genetics and Neuropsychology helped us to improve our understanding of ADHD?

In chapter 11 the hypothesis that ADHD-only children with a particular allele of the gene which controls the D4 Dopamine receptor (7-repeat), considered a risk allele for ADHD-only, were more impaired on neuropsychological measures than the group of ADHD-only without the risk allele was tested. For this reason, the performance of 10 ADHD-only children with the 7-repeat allele, 21 ADHD-only children without the 7-repeat allele and 31 Controls was compared. It was found that the two groups of ADHD-only did not significantly differ on any neuropsychological measure. However, ADHD-only children without the 7-repeat allele were more impaired, compared to Controls. The ADHD-only group with the risk allele was not significantly different from controls**.** This result, actually, is line with what found by Swanson et al. (2000) who proposed a

Stroop task, a Cued-detection task and a Go-change task. In addition, Manor et al. (2002) showed that ADHD children without 7-repeat allele performed more poorly than ADHD with 7-repeat allele on the TOVA battery (Test of Variables Of Attention).

These two results need to be integrated with those obtained by Langley et al. (2004) administering a Matching Familiar Figure Test (MFF), a Continuous Performance Test (CPT), a Go/No Go test and a Stop Task. They showed that the two ADHD groups did not differ on the Go/No Go and on the CPT, but they were different on the MFF and on the Stop Task (ADHD with 7-repeat performed more poorly than ADHD without 7-repeat allele). It is necessary to remind that these two tasks were not used by the other two studies (Swanson et al 2000; Manor et al 2002), therefore it is possible that the differences between the two subgroups of ADHD must be found on other measures that is not related on Attention but on the ability to control impulsive responses when the task requires the analysis of visual details (such as for MFF).

On table 11.2 some differences are reported between Controls and the two groups of ADHD-only (with or without the 7-repeat allele). Both subgroups of ADHD-only were significantly different from Controls on SD of RTs and Omission errors on the SART, and on the total number of words recalled on the Strategic Free Recall task. Moreover, only the group of ADHD-only without the 7-repeat allele gave significantly poorer performance than controls on RTs of the Vigilance Task and SART, on the number of Omission errors on the Vigilance task and on Score! Actually, these four variables tended to measure more specifically sustained attention skills, because children had to respond quickly and accurately for a prolonged period. Finally, children with ADHD-only and the 7-repeat allele performed more poorly than controls on the Junior Hayling.

Perhaps the differences between ADHD-only without the 7 repeat allele and Controls (and the absence of difference between ADHD-only with the 7 repeat allele) could also be due to the different sample sizes of the two ADHD-only sub-sample (the group without the 7 repeat allele was larger than the group with the 7 repeat allele), therefore other studies with larger samples are needed. However, we have to underline that on the Junior Hayling the smaller group with ADHD-

only and the 7 repeat allele was significantly different from Controls. Therefore, a plausible hypothesis that needs further investigation is that a subgroup of children with ADHD-only and without the 7-repeat could be characterized by a more pronounced deficit in sustained attention, whereas the sub-group with ADHD-only and the 7-repeat allele could be impaired on tasks that require more complex and "frontal" activities.

It could be even more interestingly to perform combined neuropsychological and genetic analysis on DRD5, 5HTT and CALCYON alleles because, as shown by a genome-wide scan of Fisher et al. (2002), these genes were likely to be implicated in the aetiology of ADHD.

12.5 Quantitative and qualitative differences between ADHD-only and ADHD+RD

So far we have not considered the comparison between ADHD-only and ADHD+RD groups. It is useful to conduct an exploratory post-hoc comparison to obtain a hypothesis as to any possible qualitative difference between the two groups for testing in future studies. Following the schema of the cognitive processes reported on table 12.2, the first cognitive domain that we analyse is Energizing Responses. In this cognitive domain there was no additive effect of ADHD and RD for children with ADHD+RD (results are related to RTs of correct responses on the SART reported in chapter 8): children with ADHD+RD performed in the same way as children with RD-only. Other qualitative differences between ADHD-only and ADHD+RD were found concerning visuo-spatial and counting processes. On two tasks of the TEA-Ch (Sky Search and Score, as reported in chapter 9), the differences between Controls and the two "pure" disorders (ADHD-only and RD-only) were significant, but not between ADHD+RD and Controls. This lack of significant difference between ADHD+RD and Controls was probably due to the reduced size of the ADHD+RD sample. The important message is that, at least concerning Energizing Attention processes, ADHD and RD do not add.

Another interesting set of cognitive processes that differentiate children with ADHD-only from ADHD+RD is related to the application of strategies, because children with ADHD-only use

semantic clustering strategies to recall words less frequently than ADHD+RD children do. Moreover, the same pattern was found concerning the use of strategies to perform the Junior Hayling: children with ADHD-only used efficient strategies to complete the sentences with semantically unrelated words less frequently than ADHD+RD children do.

Although not reported on table 12.2 it is important to underline two aspects where children with ADHD-only performed better than children with ADHD+RD: inductive reasoning on the visuo-spatial task (Junior Brixton), and rapid object naming. In particular, concerning inductive reasoning processes the ADHD+RD group was also significantly worse than the ADHD-only group [$F(1,51) = 6.533$, $p < .02$, $Eta^2 = .114$], so the most plausible account of the interaction is that there was a specific problem for the ADHD+RD group. They behaved as they even did not try to guess a rule governing the movements of the targets because their main problem was related to the significantly higher number of bizarre responses [$F(1,51) = 7.714$, $p < .01$, $Eta^2 = .132$]: their behaviour is very similar to the performance of patients with left prefrontal lesions (Reverberi et al., 2002) because they give more guessing responses than children with ADHD-only (as reported in chapter 7).

Secondly, concerning rapid object naming children with ADHD+RD were significantly slower than children with ADHD-only, as Rucklidge and Tannock (2002) found. According to Tannock, Martinussen and Frijters (2002) reported that Rapid Object Naming task requires the activation of left inferior frontal and temporal cortex, therefore our hypothesis is that children with ADHD+RD could be characterized by a dysfunction in the left inferior prefrontal cortex. Concerning children with ADHD-only, their impairments in the application of strategies and on energizing attention lead to hypothesize that they could be characterized by dysfunctions on the both sides of Dorsolateral Prefrontal Cortex: the LDPFC may causes a strategy application disorder, whereas the RDLPFC could be responsible of their Energizing Attention deficit.

In summary, considering the different postions present in the literature concerning the interpretation of the comorbidity between ADHD and RD our data support the hypothesis that concering Energizing Attention and Vigilance/Monitoring children with ADHD+RD follow the

phenocopy hypothesis proposed by Pennington et al (1993); however these tasks required the rapid naming of digits, therefore our proposal could not be conclusive. Secondly, on Left Prefrontal tasks, such as Letter Fluency and Junior Brixton, we propose that ADHD+RD is a different subtype of ADHD as Purvis and Tannock (2001) claimed.

12.6 Differences between ADHD and RD on Attention and Executive Functions

In order to define and to separate more clearly the differences between ADHD and RD on Attention and Executive Functions the two groups with a "pure" disorder has been selected: ADHD-only and RD-only. This strategy was adopted also because the MANOVAs (ADHD by RD) previously performed and presented on above chapters did not help to find all specific differences between ADHD-only and RD-only children.

From this battery it is possible to obtain seven indexes on Attention, in particular Attention and Visuo-spatial Attention: none of these measures differentiated ADHD-only from RD-only. This important result clarifies, that between ADHD-only and RD-only there are no differences concerning attention performance. Therefore, it is not useful to investigate Attention as one of the key aspects that differentiates children with ADHD from children with Reading Disorder.

Hopefully a more promising area of investigation is Executive Function. From the neuropsychological battery of study 2 it is possible to distinguish three main areas of Executive Functions: Inhibition, Set-Shift and Strategy application. Related to Inhibition four measures were considered: Commission errors on the SART, Stroop errors, Walk Don't Walk and Opposite Worlds performance. On these variables a MANCOVA was performed to find possible differences between ADHD-only and RD-only: the number of Commission errors of the SART [$F(1,75) = 6.837$, $p < .02$, $Eta^2 = .086$] and the performance on the Opposite Worlds test [$F(1,75) = 6.692$, $p < .02$, $Eta^2 = .088$]: the group with RD-only performed worse than the group with ADHD-only. Both tasks required the rapid naming of digits, but these measures are referred to the capacity to inhibit an incorrect response. Although the inhibitory impairment was unexpectedly found in children with

RD-only and in those with ADHD-only we cannot claim that children with RD-only present an inhibitory deficit because the two groups did not differ on the other inhibitory measures and also it is likely that this result is actually dependent on the specific type of the task - rapid naming of digits - in which children with RD are particularly impaired (Moore & Andrade, 2001).

A second area of Executive Function assessed by the neuropsychological battery is Set-shifting. We argued that the difference of RTs in the Counting conditions (Stars and Digits) of the Number Stroop task could be a measure of Set-shift since children must rapidly change their mental set: inhibiting an automatic response (naming digits) and producing a more controlled one. Related to this variable ADHD-only and RD-only children were significantly different [$F(1,75) = 5.569$, $p < .05$, $Eta^2 = .071$] because ADHD-only children were more affected by the presence of the digits and they found more difficulties to shift their responses; on the other hand children with RD-only were completely unaffected by the presence of digits (data are presented on table 12.2).

Furthermore, on the Junior Hayling (Total Score of Section B) there was a trend toward significance [$F(1,75) = 3.386$, $p < .06$, $Eta^2 = .050$] because, children with ADHD-only performed more poorly than children with RD-only (data are presented on table 12.2).

In summary, on Set-Shifting processes children with ADHD-only were more impaired than children with RD-only.

Finally, as far as the Strategy application is concerned, two measures were considered: the speed and the type of responses at the Junior Hayling and the increase of words recalled in clusters in the Strategic Free Recall task. A MANCOVA on these two measures revealed that the difference between ADHD-only and RD-only on the two variables of the Junior Hayling [(RTs of u-responses)-(RTs of c+s responses)] and [(ur+ul+url)-u responses] was not significant ($p > .15$) but on the use of clustering strategies on the Strategic Free Recall Task, there was a significant difference between children with ADHD-only and with RD-only [$F(1,75) = 6.028$, $p < .02$, $Eta^2 = .076$], because children with ADHD-only were not able to increase the proportion of words in clusters from List 1 to List 3.

In conclusion, no differences between ADHD-only and RD-only were found on Attention processes, but there were specific differences on some measures of Executive Function, namely on Set-Shift and on partly on Strategy Application, whereas we did not find clear differences between ADHD-only and RD-only on Inhibitory measures, with the exception of a more impaired performance of the RD-only group concerning the Commission errors on the SART and Opposite Worlds, probably due to the difficulties of verbal processing of children with RD.

12.6.1 How the SAS model can explain the ADHD symptoms?

The operation of the SAS is thought to be necessary for appropriate behavior in situations that involve planning and decision making, error correction, contain novel sequences of actions or technically difficult actions, and when the overcoming of a strong habitual response is required (Norman & Shallice, 1986).

Considering the SAS model, the most important result of the current study is that the group of children with ADHD-only were not pervasively impaired in the inhibition of strong habitual responses (see commission errors on the SART and the errors on the Number Stroop). Moreover, considering strongly activating responses, such as in the Junior Hayling, the results were not clearly indicative of a specific impairment in children with ADHD, because in study 2 the accuracy on the Junior Hayling did not discriminate children with ADHD from those without ADHD. However, if one considers a more refined measure, such as the speed of giving strategic responses in the Junior Hayling, the effect of ADHD is significant. In other words, according to the present data, ADHD could be seen as disorder in the application of strategy, rather than a deficit of inhibiting strong habitual responses.

A second issue related to the application of the SAS model is the results obtained in the Junior Brixton. In study 2 children with ADHD-only did not make a significant number of errors, compared to ADHD+RD, however the only measures that was sensitive to the presence of ADHD was a particular type of perseveration that was due to the inability to suppress a triggered responses

from the environment, rather than a perseveration due the difficulty to cognitively inhibit a previous visuo-spatial rule.

Other factors, different from those described in the SAS, that may have affected the performance of children with ADHD are related to the capacity to efficiently allocate energetics in order to respond quickly and consistently to the stimuli proposed. Although the SAS model is able to explain many characteristics of children with ADHD because they present several EF deficit, it is not sufficient to explain all the complexity of the phenomenon, because, for instance, ADHD children are also characterized deficit in the active maintenance of the vigilance. Therefore the SAS model may have to consider also these issue in order to be able to explain the complexity of the frontal lobe functioning.

12.7 Discussion of the main neuropsychological theories on ADHD

In the past decade, different refinement of the theories of causal mechanism for ADHD were proposed, emphasizing neural pathways and neuropsychologic processes (Barkley 1997; Berger and Posner 2000; Castellanos and Tannock 2002; Nigg 2001; Sagvolden et al, (2005); Sergeant et al 1999). These theories represent a blend of classic neuropsychology and contemporary and classic cognitive science, address emotion and motivation as well as cognition, and increasingly address presumed neural instantiation of the relevant mechanisms. These neuropsychological theories differ in important ways. Barkley (1997) provides a sophisticated account of the development of executive functions and regulatory control involving a range of interrelated abilities subserved by regions of prefrontal cortex and associated connections in thalamus and basal ganglia (also see Pennington and Ozonoff 1996; Schachar et al 1993). Sergeant and colleagues (1999) detail a state regulation or energetic conception of ADHD, which emphasizes physiological and performance data, including event rate dependence of some performance deficits. Such data suggest low cortical arousal in relation to a right-lateralized noradrenergic neural system, low “activation” (a process of ongoing response readiness subserved by left lateralized dopaminergic networks), or effort (closely related

to motivation). Sagvolden and colleagues (2005) emphasized reinforcement–response abnormalities involving disrupted dopaminergic functions and secondary failure of learning, conditioning, and appetitive systems that motivate behavior. Yet in each theory the dysfunctions emphasized are believed to be part of a causal developmental pathway giving rise to the ADHD syndrome. Nigg et al (2005) and Willcutt et al (2005) emphasized executive functions as a primary illustrative theory. Sonuga-Barke (2005) explicates one of the main alternatives to the EF model of ADHD, a motivational dysfunction model in which there is disruption in signaling of delayed reward. This Delay Aversion model of ADHD is supported by both human and animal data (Sagvolden 2005). Sonuga-Barke ties the Executive Function model to one frontal–striatal circuit (prefrontal– dorsal neostriatum) and the Delay Aversion model to another (orbitofrontal–ventral striatum). Each circuit is modulated by dopamine.

It is not possible to compare the present results to the Delay Aversion model (Sonuga-Barke, 2005) and the reinforcement–response abnormalities proposed by Sagvolden (2005), because neither delay aversion situations nor reinforces were devised and proposed in this neuropsychological battery. Therefore we are aware that the current results are comparable to only some, but not all, causal theories of ADHD. These results are specifically linked to the analysis of the cognitive functioning of children with ADHD, and we cannot draw strong conclusions on the links between cognitive domain, neurological basis and behavioral characteristic, according to the model proposed by Morton and Frith (1995) concerning the description of psychopathological syndromes.

However it is possible to compare our results to predictors of the Executive Dysfunction hypothesis (Willcutt et al., 2005; Nigg et al., 2005) and the Behavior Inhibition Deficit model (Barkley, 1997). Moreover, it is possible to compare our results with those obtained by other authors (Swanson et al, 1998; Manly et al., 2001) who described the attentional functioning of children with ADHD adopting tripartite models of Attention.

12.7.1 Theories of Attention deficits in ADHD

In order to give an explanation of the attention deficit in children with ADHD Swanson et al (1998) used the model proposed by Posner and Petersen (1990) in which three attentional networks are included (Alerting, Orientation and Executive Control); whereas Manly et al (2001) proposed a model in which three different systems are described (Sustained, Selective and Executive Attention). The two models are similar as far as Alerting vs Sustained Attention and Executive Control vs Executive Attention are concerned. The Alerting measures on the Posner and Petersen's model include the performance on the CPT (speed of response and omissions) whereas Manly et al (2001) battery includes different type of tasks: Score!, Walk Don't Walk and Sky Search DT. The Executive Control system, according to Posner and Petersen's, is assessed through a Stroop Number, whereas according to Manly et al's model the Executive Attention is assessed using the Opposite Worlds task. Another difference between the two models is referred to the dual task, according to Posner and Petersen this task involves the activation of the Executive Control whereas according to Manly and collegues requires the activation of Sustained Attention. Finally, the two models differ on the third component: Manly et al (2001) consider the processes of selection of the stimuli, whereas Posner and Petersen (1990) proposed the existence of a separable mechanism controlling the orientation of the attention. Orientation does not exclude Selection, but probably the former is activated before the latter, when a subject has to select a particular set of stimuli and to exclude others.

Following the model proposed by Posner and Petersen (1990), Swanson (Swanson, Posner et al., 1998) claimed that children with ADHD are mainly characterized by a deficit in the Alerting and Executive Control systems, whereas they are spared in the Orienting system. Therefore, on this thesis, ADHD is characterized by a dysfunction of on Right Prefrontal Cortex and on Anterior Cingulate Gyrus, in conjunction with localized impairments in Basal Ganglia, and they are spared in the Superior Parietal Cortex.

Manly et al (2001) hypothesize that children with ADHD are characterized by a deficit in Sustained Attention and Executive Attention, and they are unimpaired concerning Selective Attention.

In order to understand the differences between the two models concerning the attentional processes, and the proposal derived from the current study, table 12.4 shows a schematic representation of the related attentional tasks.

Table 12.4

Schematic representation of the categorization of attentional tasks

Measures	**Posner**	**Manly**	**Current Study 2**
RT responses	Vigilance/Alert		Energizing responses
Omissions	Vigilance/Alert		Vigilance/Monitoring
Sky Search		Selective	Visuo-spatial
Score		Sustained	Counting
Opposite Worlds	Executive	Executive	Set/Shift
Sky Search DT		Sustained	Visuo-spatial
Walk Don't Walk		Sustained	Inhibition

The current study used a comprehensive neuropsychological battery that could test these two competing models. On all measures, apart from the Sky Search Dual Task, children with ADHD performed more poorly than Controls. Their normal performance on Sky Search Dual Task has been considered a confirmation of the absence of a specific Sustained Attention deficit because in this task ADHD children were more activated by the execution of two tasks at the same time, and they performed better than when assessed in the two sub-tasks separately (Sky Search and Score). Following the description proposed by Stuss et al (2005) these attention processes could be included into the domain of Energizing responses. Therefore, according to our data, children with ADHD (both ADHD-only and ADHD-RD) present an Energizing response deficit. This proposal fits also with Sergeant et al (1999) who claimed that children with ADHD present a State Regulation deficit. According to Sergeant et al (1999) children with ADHD present a problem in maintaining adequate effort during task execution and this deficit may cause dysinhibitory behaviours.

Poor performance of children with RD on Energizing and Visuo-spatial tasks are probably due to their slowness in verbal processing, because the tasks require to rapidly name or to count

digits. However, in order to confirm this proposal it is necessary to perform other studies comparing ADHD and RD, using other tasks that did not require verbal processing, but sustained attention on other type of stimuli (geometrical shape, pictures and so forth).

From an anatomical point of view, there are convergent proposals (Swanson et al., 1998; Stuss et al., 1995; 2005) that Energizing Responses processes are primarily controlled by the Anterior Cingulate, therefore it is possible that children with ADHD may have a dysfunction in their Anterior Cingulate, as also postulated by neuroimaging studies (Castellanos et a, 1996; Giedd et al, 1996).

Another cognitive process described in the two models of attention here discussed (Swanson et al., 1998; Manly et al, 2001) about ADHD is the Executive Control of Attention. According to both groups of research this term refer to the capacity to control conflicting responses, inhibiting automatic, but incorrect, responses and producing non automatic responses. The most commonly used paradigm to test this cognitive process is the classical Word-Color Stroop task. Swanson et al (1998) reported that children with ADHD gave poor performance in this type of task. Manly et al (2001) tested this cognitive process using a subtest of the TEA-Ch, Opposite Worlds, in which the children have to name the "contrary" of a series of digits ("one" when they see 2, and "two" when they 1).

Our battery includes a Number Stroop task and the Opposite World test. The main problem of these task is that they both imply the decoding of digits: the Number Stroop task actually required the capacity to control the interference of digit processing, whereas the Opposite World task required the capacity to process the digits and giving a response different from what was presented on the cards. This clarification is necessary because our sample included also children with RD whose verbal processing of digits is a key aspect of their deficits. Our results showed that children with ADHD (ADHD-only and ADHD+RD) are impaired on both measures, whereas children with RD-only were not impaired in the RT of the Stroop effect because, in line with our hypothesis, their counting processes were not affected by the presence of digits.

These measures of Executive Control of Attention according to Manly et al (2001) imply the capacity to control inferences and to produce of a non-automatic, but rapid, responses. Therefore Opposite Worlds and the RT of the Stroop Effect require rapid shift therefore they are included into the domain of Set-shift. Moreover, Set-shift includes also the score on the Section B of the Junior Hayling and the Perseverations on the Junior Brixton. The Junior Hayling-B correct responses require a series of cognitive processes that are very similar to RT of Stroop Task and Opposite Worlds: the inhibition of an automatic responses (the missing word of the sentence) and the rapid activation of non automatic response (a semantically unrelated word). Whereas the Perseveration on the Junior Brixton is a measure of the difficulty to shift from an abstract spatial rule that explained the movement of the target for a certain series of stimuli, to another spatial rule. According to our description Set-Shift includes all these type of measures, although the Perseveration on the Junior Brixton does not require the control of conflicting responses, therefore it is possible that the deficit found in children with ADHD concerning Executive / Control Attention may be due to a more general impairment in cognitive flexibility for a possible dysfunction in their Dorsolateral Prefrontal Cortex.

The two models of attention, proposed by Posner and Petersen (1990) and Manly et al (2001) differ with respect to the third component: the former includes the orientation of attention toward the stimuli that must be processed (this operation is mainly controlled by the superior parietal cortex). Whereas Manly et al (2001) consider the process of selection of the stimuli that prepare the cognitive system for a deeper analysis of the targets and the "exclusion" of the non-targets. Actually, one of these two activities does not exclude the others, because in a more comprehensive model of attention, it is possible that the orientation is just activated before the selection. They could be two different stages of the same attentional activity. Manly et al (2001) did not indicate a possible localization of selection processes of visual stimuli, therefore we cannot draw any conclusion about the attentional network that could controls Orientation/Selection.

As far as our results on ADHD or RD children are concerned, the parietal lobe functioning (not specifically Orientation of attention) was tested only in study 1: a mental rotation task was used to compare the performance of children with ADHD to Controls. No difference was found between the two groups, therefore we confirm that, in this respect, the parietal lobe is spared in children with ADHD. This result is also confirmed by Swanson et al (1998) who used a RT task in which children have to detect peripheral stimuli using the information from an arrow presented in the centre of the screen. Their results revealed that ADHD children did not present any deficit of orientation.

The selection process of the stimuli could be executed only if the orientation is efficient. According to our results both children with ADHD and RD (and ADHD+RD) gave poorer performance than Controls on the visual search task (target cancellation). Manly et al (2001) did not find this result; their group of ADHD children performed like normal controls. This is unclear but it is possible that, since Sky Search is a short task and does not require the inhibition of irrelevant stimuli, the task does not require sustained or executive attention. Moreover Sky Search task does not contain verbal stimuli that must be processed, so children with RD were not disadvantaged. Therefore there are no other confounding factors that could explain their impairment. The crucial cognitive factor that could explain the quality of the performance of the ADHD group is the capacity to carry out a strategic visual search, because the measure is the time to detect a target. A possible explanation of the impairment of children with RD is that they may present a problem of focused attention and they are not able to control visual peripheral distracters (Facoetti et al., 2003; Lorusso et al., 2004). By contrast, children with ADHD may be impaired because they were not able to organize a strategic search of the stimuli and they spent more time looking at the sheet before finding a target, as previously demonstrated by Marzocchi and Cornoldi (1998). These interpretations are merely speculative but they give the possibility in testing competing hypothesis about the functioning of selective attention using visuo-spatial stimuli. For instance, it would be interesting to control the localization of the stimuli on the sheet in order to test if children with RD are slow because they are disturbed by peripheral stimuli, whereas it could be interesting to analyse

the modality of the visual search in children with ADHD to test if their search strategy could be the reason of their poor performance.

12.7.2 Theories of Executive Function deficits in ADHD

One of the most promising areas of neuropsychological investigation in children with ADHD is related to the Executive Functions (EF) researches. Since the Nineties many papers has been published on the relationships between ADHD and EF (for a review, Pennington and Ozonoff, 1996; Sergeant et al., 2002; Willcutt et al., 2005) but it is still controversial what is the actual impairment of ADHD, even following this neuropsychological approach. An important meta-analysis (Pennington & Ozonoff, 1996) divided Executive Functions into five domains of activities: Inhibition, Cognitive Flexibility, Working Memory, Planning and Fluency. The authors (Pennington & Ozonoff, 1996) concluded that ADHD is characterized by an EF impairment, in particular of Planning and Inhibition, with partial sparing of Fluency. Following the same distinction into five activities, Sergeant et al (2002) claimed that ADHD is characterized by an impairment of EF in particular in Planning (measured with Tower tasks). Whereas inhibitory deficits were not specific to ADHD, because, according to Sergeant et al (2002) dysihnibtion was found also in children with Oppositional Defiant Disorder or Conduct Disorder. A further less robust effect found in ADHD was related to cognitive flexibility, actually Sergeant et al (2002) considered only the perseverative errors on the Wisconsin Card Sorting Test. This measure was quite sensitive to discriminate ADHD from controls, in particular in the younger groups of children, but it is more sensitive to differentiate High Functioning Autistics (HFA) from controls. The third measure that, according to Sergeant et al. (2002), discriminates ADHD from normal control children is Phonemic (not Semantic) Verbal Fluency. Actually in the comparison studies between ADHD and Controls, Learning Disorders and IQ measures were rarely taken into account; therefore the discrimination property of Verbal Fluency tasks are not clear yet. Finally, concerning Visual Working Memory performance of

ADHD, Sergeant et al (2002) considered only the results obtained on the Self-Ordered Pointing Task (Petrides et al., 1982) and they concluded that it is not clear if children with ADHD present an impairment on this cognitive domain.

More recently, Willcutt et al (2005) published a comprehensive meta-analysis (168 studies) of the main tasks used to assess EF in children with ADHD, categorized into six different cognitive processes: Response Inhibition (CPT: Commission Errors, Change Task: SSRT), Vigilance (CPT: Omission errors), Set-shifting (WCST: Perseverative errors; Trailmaking test: Part B), Planning (Tower of London/Hanoi, Porteus Maze, Rey-Osterreith Complex Figure Test - ROCFT), Verbal Working Memory (Sentence Span task, Digit Backward), Spatial Working Memory (Self Ordered Pointing Task, CANTAB: Spatial Working Memory task). The overall weighted mean effect size was d = .54. The highest value was found on the Tower of Hanoi (d = .69) and the lowest value was found on the ROCFT (d = .43). Using the effect sizes values reported for each task, we calculated the average effect sizes of the six cognitive domains described by the Authors (Willcutt et al (2005). The mean effect sizes of the cognitive processes were the following: Response Inhibition = .56, Vigilance = .64, Set-shift = .51, Planning = .55, Working Memory = .59.

Combining the description reported by Willcutt et al (2005) and the tasks used in our study 2, we calculated the effect sizes of the separated cognitive domains, in order to compare our results with the meta-analysis published by Willcutt et al (2005).

Following the table 12.2, concerning our neuropsychological battery, we calculated mean effect sizes (difference between each clinical group and Controls) according to Cohen (1988) for each groups (ADHD-only, RD-only, ADHD+RD), and we reported the values on table 12.3 (according to Cohen (1998) d = .20 - .40 is considered a low effect, d = .41 – .80 is considered a medium effect, d = .81 or more is considered a high effect). The mean effect sizes were calculated using the tasks reported on table 12.2. The results concerning the seven cognitive processes are reported on table 12.5.

Table 12.5

Effect sizes of the EF Cognitive Processes.

Cognitive processes	**ADHD-only**	**RD-only**	**ADHD+RD**
Energizing Attention (+Vigilance)	0.56**	0.77**	0.85***
Visuo-spatial & counting Attention	0.61**	0.82***	0.56**
Inhibition	0.39*	0.70**	0.82***
Memory	0.64**	1.19***	1.39***
Set-shift	0.48**	0.28*	0.49**
Strategy application	0.52**	0.04	0.13
Verbal Fluency	0.13	0.13	0.39*

Legend = * Low effect size (0.20-0.40); ** Medium effect size (0.41 – 0.80); *** High effect size (above 0.81), Cohen (1988).

Table 12.4 gives an overview concerning the results already discussed in paragraph 12.2. On Energizing attention all groups were impaired, whereas the poorest performance was given by ADHD+RD. On Visuo-spatial and counting attention tasks all groups were impaired but in this case the most impaired group was that with RD-only. On inhibitory processes children with RD were the most impaired groups (although children with ADHD-only were moderately impaired). On memory, all clinical groups give poor performance although the two groups with RD were the most impaired. On Set-shifting both groups of children with ADHD were impaired whereas children with RD-only were spared. On Strategy application only children with ADHD-only gave a poor performance. Finally on Verbal Fluency only children with ADHD+RD gave a poor performance, although the effect size was low.

Although the meta-analysis carried out by Willcutt et al (2005) did not consider any of the tasks included in our neuropsychological battery (therefore any comparison is forced) we can try to compare the effect sizes obtained in the current research to those obtained by Willcutt et al (2005) considering Energizing Attention, Response Inhibition and Set-shift (We cannot compare the our

other cognitive measures because they are different from those reported by Willcutt et al (2005). Moreover, for comparing similar groups of subjects (our study vs Willcutt et al, 2005) we consider all children with ADHD (ADHD-only and ADHD+RD). On Energizing Attentional tasks (including Vigilance) according to our data all children with ADHD have an effect size of d = 0.70, whereas Willcutt et al (2005) found 0.64. On Response inhibition we found d = .61 whereas Willcutt et al (2005) d = 0.56. Finally on Set-shift we found d = 0.49 whereas Willcutt et al (2005) d = .51. It is clear that the current results are very similar to what Willcutt et al (2005) found summarizing the results of 168 studies on ADHD and EF. This comparison gives us the information that the performance of our groups of children with ADHD was in line with what the current literature has found in the last decades of research of Executive Function.

It is necessary to be precise that, following the description proposed by Willcutt et al (2005) about the separate sub-components of EF, we observe clear overlaps between attention and EF models. Firstly, Sustained Attention or Vigilance described in the attention models (Posner & Petersen, 1990; Manly et al., 2001) are the same processes thought to belong to the Executive Function domain. Secondly, the domain concerning Executive Control of Attention includes measures using to analyze the ability in Set-Shifting activities: both measures require the control of interferences and of automatic responses. Therefore the anterior attention processes (Stuss et al, 1995) are the same processes described in the Executive Function models where the voluntary control of action by the subject is the crucial factor for an efficient performance. The posterior attention processes (mainly Orientation) are automatic (Corbetta & Shulman, 2001) therefore they are not included into Executive Functions models**.**

Now, considering the neuropsychological models about ADHD: Barkley (1997) focusing on Response Inhibition deficit; Sergeant et al (1999) on the defective regulation of cognitive energetic processes; Swanson et al (1998) on the impairment on Alerting and Control of Attention; and Manly et al (2001) on the deficit on Sustained and Executive / Attention, we try to give a general explanation integrating our results with previous models.

As far as the model proposed by Barkley et al (1997) our results do not confirm the presence of a generalized impairment in response inhibition, but we have found a deficit in Energizing Attention that could overlap the State regulation deficit proposed by Sergeant et al (1999). Energizing Response and Vigilance impairments are present, because ADHD performance is significantly poorer than the performance of Controls, and their slower RTs and lower accuracy are not affected by problems in processing digits, as shown by children with RD (Nicholson & Fawcett, 1999). As Stuss et al (2005) underlined, an Energizing Response deficit could be due to a dysfunction in the Anterior Cingulate whereas a Vigilance/Monitoring impairment could be due to a dysfunction in the Right Dorsolateral Prefrontal Cortex.

Secondly, children with ADHD-only also present a deficit, although moderate, of Set-Shifting and of Strategy Application. Both cognitive processes may be controlled by the Left Dorsolateral Prefrontal Cortex (Stuss et al., 2000; Stuss et al., 1998, respectively).

Our hypothesis is that multiple areas of dysfunction could be characteristic of children with ADHD-only: Energizing Response (ACG), Vigilance/Monitoring (RDLPC) Set-shift (LDPFC) and Strategy Application (LDPFC). This proposal also fits with recent ADHD models proposed by Sonuga-Barke (2005) and by Nigg et al. (2005), who claim that children with ADHD may present multiple and independent pathways of impairment: Executive Dysfunction and Delay Aversion.

Actually, our proposal has two important differences compared to these recent models: Sonuga-Barke (2005) and Nigg et al (2005) also considered delay aversion performance, therefore our study could not be exhaustive and could not helps us to fully understand the psychological functioning of children with ADHD. The second difference is that we have separated out two different cardinal components of the executive dysfunction in children with ADHD: Energizing Responses and Vigilance/Monitoring from Set-shift and Strategy Application. Therefore, also among the domain of Executive Function, we postulated that it is possible that these two cognitive domains (Energizing attention vs Set-shift and Strategy Application) may be independently impaired in children with ADHD.

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