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THE RELATIONSHIP BETWEEN PRAXIS AND LANGUAGE

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS IN ALPHABETICAL ORDER

AAT = Aachen Aphasia Test

AD = Alzheimer’s Disease

AM = Attentional Matrices

ATL = Anterior Temporal Lobe

BJLO = Benton Judgment of Line Orientation

CAS = Cologne Apraxia Screening

CBD = Corticobasal Degeneration

CBS = Corticobasal Syndrome

dPMC = dorsal Preomotor Cortex

FAB = Frontal Assessment Battery

FDG-PET = Fluoro-deoxy-glucose Positron Emission Tomography

fMRI = functional Magnetic Resonance Imaging

GIT = Goldenberg Imitation Test

GIT_F = Finger gestures subtest of the Goldenberg Imitation Test

GIT_H = Hand gestures subtest of the Goldenberg Imitation Test

HP = Healthy Participants

IA = Ideational Apraxia

IFG = Inferior Frontal Gyrus

IMA = Ideo-Motor Apraxia

IMAT = Ideo-Motor Apraxia Test

IML = Imitation of gestures with the upper Limb

IMO = Imitation of Oral gestures

IPL = Inferior Parietal Lobule

IPS = Intraparietal Sulcus

LQ = Laterality Quotient

MF = Meaningful gestures

MFD = Meaningful Distal gestures

MFP = Meaningful Proximal gestures

ML = Meaningless gestures

MLD = Meaningless Distal gestures

MLP = Meaningless Proximal gestures

MMSE = Mini-Mental State Examination

MNI = Montreal Neurological Institute

MOU = Multiple Object Use

MPS = Mechanical Problem Solving

MT = visual Motor area

M < P/C = Manipulation < Purpose or Context of use

NAVS = Northwestern Assessment of Verbs and Sentences

NAVS_N = Naming subtest of Northwestern Assessment of Verbs and Sentences

NAVS_C = Comprehension subtest of Northwestern Assessment of Verbs and Sentences

NoDiss = No Dissociation

PCA = Posterior Cortical Atrophy

PET = Positron Emission Tomography

pMTG = posterior Middle Temporal Gyrus

POU = Pantomime of Object Use

POU_L = Pantomime of Object Use with the upper limb

POU_O = Pantomime of Oral Object Use

PPT = Pyramids and Palm Trees test

P/C < M = Purpose or Context of use < Manipulation

RAVLT = Rey Auditory Verbal Learning Test

ROCF = Rey-Osterrieth Complex Figure

rTMS = repetitive Transcranial Magnetic Stimulation

SAT = Semantic Association Task

SAT_CA = Categorical Association subset of the Semantic Association Task

SAT_EA = Encyclopedic Association subset of the Semantic Association Task

SAT_FA = Functional Association subset of the Semantic Association Task

SAT_VEA = Visual-Encyclopedic Association subset of the Semantic Association Task

SC = Sentence Comprehension

SD = Semantic Dementia

SOU = Single Object Use

SPL = Superior Parietal Lobule

SPM = Statistical Parametric Mapping

STIMA = Short Test for Ideo-Motor Apraxia

TMS = Transcranial Magnetic Stimulation

TOF = Type of Gesture

VBLSM = Voxel-Based Lesion-Symptom Mapping

VCT = Visual Completion Task

VCT_A = Animal subset of the Visual Completion Task

VCT_O = Object subset of the Visual Completion Task

VLT = Verbal Learning Task

vPMC = ventral Premotor Cortex

WC = Word Comprehension

ABSTRACT

Linguistic and praxis deficits often co-occur in patients with stroke-related left hemisphere lesions and in those with neurodegenerative diseases, especially Semantic Dementia. Many behavioral and neuroimaging studies involving both patients and healthy participants revealed that these two cognitive abilities are at least partially supported by common neural pathways, but the interpretation of the interaction between language and praxis depends on which cognitive aspects are examined. For this reason, three studies involving different praxis and linguistic tasks were conducted.

First, cognitive processes that enable imitation of meaningless and meaningful gestures were studied in left hemisphere stroke patients through performance obtained in a general standardized battery for aphasia, in verb naming and comprehension tasks, and in a semantic association task (which included various types of semantic association, e.g. matching objects that could be used together in the same action). Patients were significantly more affected in the imitation of meaningful, as opposed to meaningless, gestures. Higher scores in imitation of meaningful gestures were significantly predicted by better performance on the semantic association task when participants were required to associate objects that could be used together to perform a familiar, meaningful action.

A second study investigated neural correlates of three distinct types of conceptual object knowledge (i.e. manipulation, purpose and context of use), in a group of neurodegenerative patients. In association with disproportionate behavioral responses on each type of object knowledge, three distinct patterns of hypometabolism emerged. Specifically, manipulation knowledge significantly correlated with the left angular gyrus, and left posterior middle and inferior temporal areas, whereas purpose and context of use significantly correlated with the left temporal pole, the left fusiform gyrus and left anterior temporal areas.

Finally, the role of manipulation and function knowledge in object use was investigated in patients with Alzheimer’s disease. Poor performance in matching pictures of objects that could be manipulated in the same way significantly predicted the probability of having a deficit in object use.

Conversely, flawless performance when matching pictures of objects that shared the same function, significantly predicted positive outcomes in objects use tasks.

Taken together, results show that action semantic knowledge, which encompasses knowledge about which objects can be used together in a purposeful action as well as manipulation knowledge, may be the joining element where action and language interact and overlap.

CHAPTER 1. THEORETICAL OVERVIEW

1.1 THEORETICAL MODELS OF PRAXIS

1.1.1 Definition of Apraxia and its forms: Liepmann's model

Apraxia can be defined as a disorder of skilled movements execution, causing inability or a reduced capacity of programming and executing voluntary movements, which cannot be explained by presence of weakness, primary sensory or motor deficits (such as paresis, ataxia, or trembling), intellectual deterioration or language deficits (such as poor comprehension). Core features of this disorder are difficulties in imitation of (meaningful or meaningless) gestures, execution of pantomime of tool use, and correct tool application or manipulation. One important characteristic of apraxia is that a patient may be perfectly able to execute a gesture reflexively (e.g. he/she can correctly use a fork to eat when food is served to him/her), but not consciously (e.g. he/she cannot demonstrate how to use a fork during an experimental task). Liepmann (1905, 1908) first described a theoretical model for movement execution that could account for three distinct types of apraxia based on the level at which the cognitive process is disrupted. The correct execution of a movement, in fact, requires at least three steps: motor planning, motor programming and final execution. The first step entails picturing the intended action. To create this image, various types of sensory information (e.g. visual, acustic, tactile) are integrated. These sensory representations, called "residuals" of movements, are localized in associative posterior parietal areas. A deficit at this cognitive level causes Ideational Apraxia (IA), which consists of defective performance in programming a complex sequence of gestures. The second step entails creating a motor program, which consists of a specific motor and kinesthetic innervation pattern. In this step, the image of the intended action is transferred from associative parietal areas to primary motor areas and then translated into a motor program. This process occurs through access to "motor engrams", defined as spatio-temporal memories (e.g. deciding upon the correct configuration of the hand to grasp a hammer and the amplitude of the arm movement required to punch a nail) that control purposeful skilled movements. A disruption in the transition from the motor planning to the motor innervation characterizes the variety of apraxia Liepmann initially called “motor apraxia” and later “Ideo-Motor Apraxia” (IMA). A failure at this level causes predominant deficits in the imitation of gestures, but also spatial or temporal errors during the execution of the movement. Spatial and temporal errors correspond to an impairment in the timing, sequencing and spatial organization of gestural movements (i.e. a degraded internal or external configuration of the gesture, trajectory errors). The last step, which leads to the correct execution of the action, may be impaired due to damage to the innervational-kinetic engrams. In contrast to the motor engrams, the innervational-kinesthetic engrams are conceived as physiological, rather than psychological, entities. They consist of kinesthetic sensations, i.e. traces of the motor innervation that are located in the sensorimotor cortex of both hemispheres, that code for the innervatory patterns to accurately execute the movement. The consequent disorder is called limb-kinetic apraxia, which can be defined as erroneous speed or rhythm during the execution of the movement, which in turn causes inaccuracy. According to Liepmann, ideational apraxia is caused by left posterior temporo-parietal lesions, in particular on the caudal part of the left parietal lobe. Ideo-Motor apraxia can be observed following the development of parietal lesions, which disconnect the motor engrams (stored in the caudal part of the left parietal lobe) from the premotor and motor areas that control purposeful skilled movements. In addition, infarction of the corpus callosum can cause isolated apraxia for the left hand, as motor engrams stored in the left hemisphere may be disconnected from motor areas in the right hemisphere. Finally, limb-kinetic apraxia is caused by lesions to those sensory motor areas contralateral to the affected limb. Whereas both ideational and Ideo-Motor apraxia have been widely studied, the topic of limb-kinetic apraxia has been largely neglected. In fact, its very existence has been questioned (Denes et al., 1998). However, specific studies have revealed that limb-kinetic apraxia cannot only be observed in neurodegenerative diseases such as Parkinson’s disease (Quencer et al., 2007), Progressive Supranuclear Palsy (Leiguarda et al., 1997) and Corticobasal Degeneration (Leiguarda et al., 2003), it can be distinguished from other extrapyramidal features such as rigidity and bradykinesia. This dissertation aims to explore the cognitive mechanisms underlying motor planning and the motor control aspects of actions as well as their relationship to action and semantic knowledge. Thus, the focus will be on Ideational and Ideo-Motor forms of apraxia.

1.1.2 Characterization of Ideational Apraxia (IA) and Ideo-Motor Apraxia (IMA)

The distinction between IMA and IA, according to Liepmann’s model, is based on the presence of a deficit in executing a simple action versus a deficit in programming the logical sequence of a complex action. Whereas patients with IMA are impaired in single object use, patients with IA are unable to program the correct sequence of an action (e.g. when trying to light a candle, they light the match before putting the candle on a candlestick) albeit still able to perform the single steps of the action (i.e. the single object use, such as light the match or put the candle on the candlestick). However, Liepmann’s distinction was later challenged (Sittig, 1931) because every gesture, either complex or simple, may be separated into distinct movements, which require some kind of programming. Thus, IA may cause a failure not only in programming a complex action with more than one object (e.g. how to hammer a nail into a piece of wood with a tool) but also in creating the correct program of a simple action with only one object (e.g. how to use a hammer). In fact, subsequent studies (De Renzi et al., 1968; De Renzi & Lucchelli, 1988) showed that patients with IA could present not only sequence errors within a complex action (i.e. employing an object without having carried out an action that must come before, such as sealing an envelope without having put the letter inside) but also the omission (e.g. using the hammer on a piece of wood, without having picked up the nail) or misplacement (e.g. positioning the nail upside-down or hammering on the pointed end of the nail) of parts of complex actions, as well as the faulty use of single objects (e.g. using an ice scraper as a shovel to pick something up). This leads to conclude that IA is also a disorder of single object use. The two forms of apraxia can present separately in patients (De Renzi et al., 1968; Mengotti et al., 2013) and performance on tasks investigating IA (use of single objects or multiple objects to perform a complex action) and IMA (gestures imitation) may not correlate (De Renzi & Lucchelli, 1988; Lucchelli et al., 1993), suggesting that they are dissociable cognitive functions, supported by segregated neural networks. According to De Renzi (1968; De Renzi & Lucchelli, 1988), IA and IMA correspond to two distinct levels of gesture processing - a semantic level, which refers to long-term stored knowledge regarding known gestures (i.e. actions with objects and symbolic intransitive gestures, such as a wave goodbye) and an action execution level that requires motor control. An impaired performance on any task requiring retrieval of information regarding known gestures (e.g. using an object, classifying a gesture, performing familiar gestures on verbal command) allows classification of a patient as having IA. In contrast, an impaired performance on imitation tasks identifies the presence of IMA. Following Liepmann's (1908) identification of left temporo-parietal lesions, later studies identified the territory of the temporal angular artery (Foix, 1916), the superior temporal gyrus (Moorlas, 1928) or the temporo-parietal junction (Hécaen, 1972) as possible substrates of IA. Lesions underlying IMA were identified in the left arcuate fasciculus and supramarginal gyrus (disconnect between Wernicke's area and the motor association cortex; Geschwind, 1965), in the left parietal lobe (disruption of the visuo-kinesthetic motor engrams; Heilman et al., 1982) and in premotor cortices (De Renzi et al., 1980). However, De Renzi's model did not appear to properly account for the extreme variety of deficit patterns that could be observed in apraxic patients. For example, patients could be more impaired at imitating gestures than performing the same gestures on verbal command (De Renzi & Scotti, 1970; Poncet et al., 1971; Ochipa et al., 1994). Furthermore, patients' performance on the imitation of new (meaningless) gestures could dissociate from the imitation of familiar (meaningful) gestures (Goldenberg & Hagmann, 1997; Bartolo et al., 2001). Apraxia may cause not only deficits in imitation or movement execution, but also difficulties in discriminating between well-performed or improperly performed (clumsiness or using body parts as objects) gestures (Heilman et al., 1982) and in matching the picture of an object with its corresponding gesture (Bergego et al., 1992).

1.1.3 Cognitive neuropsychological models of Apraxia

Neuropsychological studies on apraxic patients have raised the question about the relationship between different aspects of an action that may be selectively disrupted. Dissociations were found between action planning, action imitation, action execution and action recognition. Furthermore, the type of gesture to be imitated, i.e. pantomime of object use (e.g. pantomiming the use of a hammer without the object), meaningful intransitive gestures (e.g. waving goodbye), meaningless intransitive gestures (e.g. putting the thumb on the forehead), meaningful tool use transitive gestures (e.g. showing how to use an hammer with the object in hand) may impact the type and degree of dissociation (Klatzky et al., 1993; Goldenberg & Hagmann, 1997; Bartolo et al., 2001; Negri et al., 2007b). Performance on all these tasks may be differentially impaired on the basis of the task presentation modality (e.g. after presenting a real object, the picture of an object or the picture of an action, or after verbal command; De Renzi & Scotti, 1970). Thus, Rothi and colleagues (1991) proposed a cognitive neuropsychological model for gesture comprehension and production as well as for the two-route models of language production and comprehension (Patterson & Shewell, 1987; Coltheart et al., 1993). The authors hypothesized that gesture imitation is supported by two distinct routes: a semantic route, which is employed when the person is required to imitate meaningful (familiar) gestures, and a non-semantic visuo-motor route which allows imitation of new, meaningless gestures through a direct visuo-motor transformation, from visual analysis to a specified motor innervation pattern. The dual-routes distinction allows quickly and efficient retrieval of previously known gestures, via the semantic pathway, as we have access to a learned gestural lexicon, which is subdivided into input and output levels responsible for recognition and execution of gestures, respectively. Cubelli et al. (2000) modified this model and further characterized the cognitive steps required between input and output lexicons (for a similar model, see also Rumiati et al., 2010). In this model, the authors added a visuo-motor conversion mechanism to represent the non-semantic route for meaningless gestures imitation. This mechanism enables the transduction of a visually coded gesture, executed by another person, in the corresponding motor program. Furthermore, the authors added a gestural memory buffer, in which both routes converge, allowing retention of a short-term representation of the motor program of the gesture to be executed. An outline of Cubelli and colleagues' model is depicted in Figure 1. Within this revised version, it is possible to account for the dissociated patterns of behavior observed by previous studies on apraxic patients. First of all, damage to the action input lexicon causes difficulties in gesture recognition, gesture comprehension or in comparison between a well-performed and an incorrectly performed gesture, with spared abilities of gestures imitation and execution on verbal command. A deficit at the level of the action semantic system, instead, causes difficulties in performing familiar gestures on verbal command and in comprehending the meaning associated with them. However, a patient with a deficit of the action semantic system should be able to correctly imitate gestures, distinguish meaningless from meaningful gestures and well-performed from clumsily-performed gestures. Damage to the action output lexicon is similar to the deficit resulting from damage to the action semantic system, but with a spared ability to associate a gesture with its meaning. A patient with deficit at the level of the visuo-motor conversion mechanism should exhibit deficits in gesture imitation, particularly for meaningless gestures. Damage to the gestural buffer causes impairment in all tasks that require gesture production, both on verbal command and on imitation, with spared abilities in gesture recognition, meaning association and performance judgments. A similar model (Goldenberg, 1995; Goldenberg & Karnath, 2006; Goldenberg, 2014), postulated different mechanisms for meaningless and meaningful gestures imitation as well, but introduced an intermediate step between perceptual representations of other bodies performing an action and the specification of motor regions controlling one's own body. According to this hypothesis, when we see a gesture performed by another individual, we require a mechanism, namely "body part coding", which decomposes the perceived gesture into combinations of a limited number of defined body parts, and matches these seen body parts with the corresponding body parts of the observer. Only then can the specification of the motor innervation pattern and the final gesture execution occur. In this view, imitation deficits in apraxic patients may also reflect an impairment of the body schema. This model can account for the observation that apraxic patients may be impaired not only in imitating gestures but also in reproducing them on a mannequin (Goldenberg, 1995).

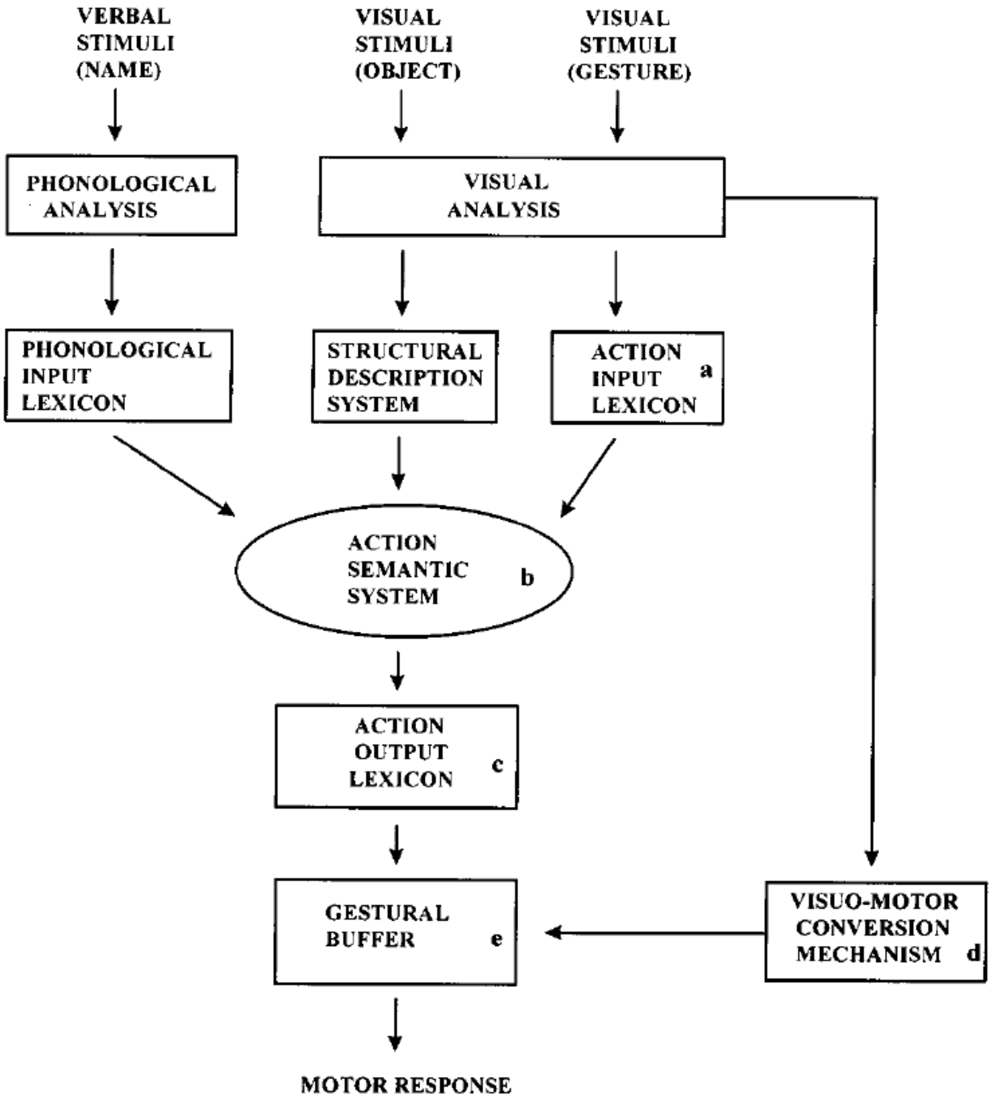


Figure 1. Outline of the modified version of Rothi and colleagues' model (1991) delineated by Cubelli et al., 2000.

1.1.4 Neuropsychological evidence of multiple routes in Ideo-Motor apraxia

According to De Renzi's definition, Ideo-Motor apraxia (IMA) is characterized by difficulties in imitating a seen gesture which is performed by another person. Numerous studies on apraxic patients showed dissociated performance between imitation of meaningful and meaningless gestures (Goldenberg & Hagmann, 1997; Bartolo et al., 2001; Tessari et al, 2007; Mengotti et al., 2013; Achilles et al., 2016) providing strong support to the dual-route model (Cubelli et al., 2000). For example, Goldenberg & Hagmann (1997) reported the case of two patients with damage to the inferior portion of the left angular gyrus who had severe deficits in imitation of meaningless gestures but spared performance in execution of meaningful gestures to verbal command and in the imitation of meaningful gestures. This pattern of deficit is compatible with that predicted by the model following damage to the output lexicon. Bartolo and colleagues (2001) investigated the performance of three left hemispheric stroke patients in several recognition and production tasks involving meaningful transitive (e.g. with real objects) and intransitive (e.g. military salute) gestures. Specifically, recognition tests included discrimination between a well-performed and an incorrectly performed meaningful transitive gesture (i.e. "is the gesture performed by the examiner correct or wrong?") and between known or new intransitive gestures (i.e. "is the gesture performed by the examiner familiar or novel to you?"). Two gesture-object matching tasks were also included to test for the identification of the object corresponding to a pantomime or the identification of the picture corresponding to a performed intransitive gesture. Six further tasks explored patients' ability to perform meaningful transitive and intransitive gestures on verbal command or in the presence of the real object; three tasks investigated imitation abilities for pantomimes (transitive meaningful gestures), intransitive meaningful and meaningless gestures. Results showed that all three patients had a relatively spared performance on all recognition and gesture-object matching tasks, suggesting intact action-input lexicon and action semantic system. Two cases showed a selective deficit in tasks requiring imitation of meaningless gestures, but were spared in production of meaningful gestures, thus indicating a selective deficit of the visuo-motor route. The third case showed a reverse pattern, with selective difficulties in meaningful gesture imitation performance as well as in production of meaningful gestures on verbal command or in object presentation, which can be attributed to damage to the lexical route at the level of the action output lexicon. Evidence for two separate mechanisms for imitation of meaningless and meaningful gestures were observed in neurologically intact individuals as well (Tessari & Rumiati 2004, Tessari et al., 2011). In fact, healthy individuals imitated familiar gestures easier and more quickly (Tessari & Rumiati, 2004) than they did novel gestures, and they attained better performance in a gesture imitation task (Tessari et al., 2011) on meaningful, symbolic gestures than on new, meaningless gestures. Furthermore, neuroimaging studies in healthy volunteers (Peigneux et al., 2004; Rumiati et al., 2005) and left brain damaged patients (Buxbaum et al., 2014) found segregated brain activation for novel gestures and for imitation of familiar gestures imitation (for an extensive description of distinct neural basis see paragraph 1.4.4). Moreover, when imitating meaningless gestures, an additional functional and neural segregation can be observed based on the specific body parts that are involved in the gesture execution. De Renzi et al. (1980) hypothesized possible dissociations between gestures executed with the hand, relative to the body (proximal motor component), and gestures executed with the fingers (distal motor component). Shallice and colleagues (2005) demonstrated that apraxic patients with defective tool use may show selective perseveration behavior for the hand or the arm movements. Tanaka & Inui (2002) conducted a functional Magnetic Resonance Imaging (fMRI) study on healthy volunteers, revealing that imitation of finger gestures was specifically related to activation in the inferior frontal gyrus of both hemispheres, while imitation of arm/hand gestures was associated with the left superior parietal regions. Consistent with these neuroimaging findings, Goldenberg & Karnath (2006) reported seven cases of left hemisphere damaged patients with selective impairment in the imitation of meaningless hand gestures, contrasted with normal performance in the imitation of meaningless gestures, and five patients with the reverse dissociation. The authors detected a clear-cut body part specificity for imitation of finger- as compared to hand gestures- in the corresponding lesion analysis. Specifically, patients with selective impairment in hand gestures had overlapping lesions in the middle temporal (including the adjacent white matter) and middle occipital gyri and in the inferior parietal lobule of the left hemisphere. In contrast, patients with selective impairment in finger gestures had more anterior overlapping lesions, in the left inferior frontal gyrus and the adjacent insular cortex, as well as in the putamen and caudate nucleus.

1.1.5 Summary and unsolved questions

Traditionally, the classification of apraxia is based on the distinction between two levels of action processing – i.e. the semantic level and the action planning and programming level – which leads to two forms of apraxia – i.e. Ideational and Ideomotor apraxia. However, a large amount of neuropsychological studies has suggested the existence of different sub-components of our ability to execute gestures, which can account for the high variability of praxis disorders that can be observed in patients. The core question, concerns the fine description of the cognitive mechanisms underlying motor programming and motor control aspects of action. The dual-routes models of action (Rothi et al., 1991; Cubelli et al., 2000) raised the importance of distinguishing between different types of gestures (meaningful intransitive gestures, meaningful transitive gestures, meaningless gestures), tasks (imitation, recognition, execution) and input modalities (verbal command, visual presentation) when aiming at an accurate evaluation of praxis disorders. The model, in fact, describes the cognitive and motor steps that are involved when we are engaged in an activity that requires to execute, imitate, pantomime or recognize gestures. Accordingly, gesture processing is supported by multiple neural pathways. Gesture imitation, which is the core deficit in patients with Ideomotor apraxia, can be disproportionately impaired on the basis of the specific gesture that is required to imitate. For example, healthy participants have better performance on meaningful symbolic (e.g. horn gesture) gestures imitation, compared to meaningless gestures imitation, suggesting that symbolic gestures are stored in a gestural memory and can be easily accessed and retrieved (meaningful superiority effect; Tessari & Rumiati, 2004). Meaningless gestures, instead, are executed through a visuo-motor conversion mechanism that translates the gesture executed by another person into the corresponding motor program. Meaningful gestures can be further subdivided into intransitive (symbolic) gestures and transitive gestures (pantomime of object use and actual object use). According to the dual-routes model, it is possible to detect dissociated patterns in the imitation of these three types of gestures (meaningful transitive, meaningful intransitive and meaningless gestures). In support to such models, double dissociated patterns were reported, obtained when patients were asked to imitate meaningless and meaningful gestures (Goldenberg & Hagmann, 1997; Bartolo et al., 2001; Tessari et al., 2007). However, there are still some aspects that need to be clarified. First, only a few studies focused on the difference between meaningful transitive and meaningful intransitive gesture imitation, even if evidence of such dissociation does actually exist (Bartolo et al., 2003; Buxbaum et al., 2007; Dressing et al., 2016). Second, according to some researchers within the dual-routes model perspective (Tessari & Rumiati, 2004), when the semantic route is disrupted, the visuo-motor route may be engaged in the imitation also of meaningful gestures. However, patients were reported with spared performance on meaningless gestures imitation (Goldenberg & Hagmann, 1997; Bartolo et al., 2001), which had actually a severe impairment in the imitation of meaningful gestures. Thus, the possible recruitment of the visuo-motor route for the imitation of meaningful gestures in patients with damage to the semantic route is still matter of debate. These interesting questions were addressed in the first study of the present work.

1.2 LINGUISTIC ABILITIES RELATED TO PRAXIS

1.2.1 Association between Aphasia and Apraxia

The association between aphasia and apraxia has been widely investigated in left brain damaged patients, as left hemisphere lesions frequently impair both linguistic and action domains. In a large cohort of 415 patients (de Ajuriaguerra et al., 1960), nearly all patients who suffered from apraxia (72 percent of patients suffered from Ideo-Motor apraxia, whereas the remaining 27 percent had ideational apraxia) were also aphasic. De Renzi et al. (1968) investigated the relationship between ideational apraxia (IA), defined as inability to demonstrate the correct use of an object, and presence of Ideo-Motor apraxia (IMA) symptoms, defined by poor performance in a gesture imitation task, and between IA and aphasic syndromes in 45 right brain damaged patients and 160 left brain damaged patients. While no right brain damaged patients failed in apraxia tests, 28 percent (n = 45) of left brain damaged patients suffered from IMA and 28 percent (n = 45) of left brain damaged patients suffered from IA. Both forms of apraxia were detected in 21 percent of patients (n = 34), whereas 14 percent of patients presented one isolated form (n = 22, of whom 11 patients suffered from isolated IMA and 11 patients suffered from isolated IA). Only four patients with IMA and two patients with IA were not aphasic, whereas 84 aphasic patients did not suffer from apraxia. These results suggest a double dissociation between aphasic and apraxic symptoms, but also point to a close relationship between IA, left hemisphere lesions and presence of aphasia. Furthermore, IA appeared in all aphasic syndromes excepting those with mild and moderate forms of Broca’s aphasia, and tended to be more strongly associated with Global and Wernicke’s aphasic syndromes. According to the authors, poor performance on IA tasks in aphasic patients may be explained by damage to an overlapping cognitive mechanism that allows association of an object to its typical features, such as its shape, color and sound (Spinnler & Vignolo, 1966; De Renzi & Spinnler, 1967). Specifically, the difficulty in associating an object to the movement that is commonly required to appropriately manipulate it may cause poor performance of IA tasks in aphasic patients. Thus, according to De Renzi et al (1968), the association between IA and aphasia suggests an overlapping cognitive mechanism, which enables the association of different aspects of an object (e.g. the typical color, the shape, the appropriate movement to make with an object). In a further study of IMA (De Renzi et al., 1980), imitation deficits were detected not only in left brain damaged patients (50 percent) but also in right brain damaged patients (20 percent); in these patients IMA was usually associated with aphasia, but very rarely observed in non-aphasic patients. However, according to the authors, the correlation between imitation performance and measure of linguistic abilities (performance on the Token test) was not sufficiently high to implicate language disorder in impairing the ability to imitate gestures. Other studies reported similar patterns of dissociation-association between apraxia and aphasia in left hemisphere lesioned patients. For example, Papagno and colleagues (1993) found that, in a large cohort of 699 patients, co-occurrence of aphasia and apraxia was the most common constellation, whereas 149 patients were aphasic but not apraxic and 10 patients showed the reverse pattern. In 57 left hemisphere stroke patients, only 6 cases presented isolated aphasia, whereas 1 patient had isolated IA and 5 cases showed isolated IMA (Mengotti et al., 2013). Weiss and colleagues (2016) detected both apraxic and aphasic symptoms in 50 percent of patients, with incidence of apraxia in approximately 70 percent of aphasic patients and presence of aphasic symptoms in quite all (93 percent) apraxic patients. This divergence between association of apraxic and aphasic symptoms and, at the same time, double dissociations between them, raises the question of whether aphasia and apraxia often present together because of anatomical contiguity of their underlying neural substrates or because they are, at least partially, supported by an overlapping cognitive mechanism. In a recent neuroimaging study, Goldenberg & Randerath (2015) explored the association between different aphasic and apraxic symptoms and common lesion substrates in patients with left hemisphere stroke. Presence of both apraxia and aphasia and regions of overlapping varied based on the specific sub-components of both disorders that were compared- i.e. pantomime of tool use, imitation of meaningless hand gestures and imitation of meaningless finger gestures were used to test for presence of apraxia, whereas the Aachen Aphasia Test battery (AAT; Huber et al., 1983, 1984) was employed to test for presence of aphasia (this battery comprises evaluation of Spontaneous Speech, Token test, Repetition, Written Language, Picture Naming, Oral and Written Comprehension). Associations between aphasia and pantomime deficits were found in 41 patients, whereas 40 patients shared both aphasia and deficits in imitation of meaningless hand gestures. Deficits in imitation of meaningless finger gestures were detected in 28 aphasic and 3 non-aphasic patients. Interestingly, deficits in pantomime of tool use and poor performance on all linguistic subtests of a neuropsychological battery for aphasia shared lesions in the medial temporal lobe. This area may represent impaired access to semantic memory, which may be exploited by both pantomime and linguistic tasks. In contrast, defective performance in imitation of meaningless gestures overlapped with poor scores on written language and Token Test in a large inferior parietal region that included the angular gyrus and supramarginal regions, which were also associated with defective pantomime. Thus, parietal areas may be the neural underpinnings of the cognitive mechanism that allows the coding of spatial relationships and their conversion into a motor planning of the intended action. This study emphasized that, when aiming at exploring possible cognitive and neural mechanisms supporting both apraxia and aphasia, researchers should consider that the way in which language and praxis domains interact is determined by the sub-components that are taken into account.

1.2.2 Linguistic abilities and imitation of Meaningful gestures

According to the dual-routes model (Rothi et al., 1991; Cubelli et al., 2000; Rumiati et al., 2010; for a more extensive description, see paragraph 1.1.3), two distinct cognitive pathways are used in the imitation of new (meaningless) actions and familiar (meaningful) actions. In particular, the execution of meaningful gestures is thought to rely on a stored semantic gestural knowledge, which allows rapid retrieval of the motor planning of the seen gesture through access to its semantic meaning (Rumiati et al., 2010). Within this theoretical framework, the close relationship between aphasia and apraxia may be explained by the potential recruiting of overlapping neural regions in both the imitation of meaningful gestures and in certain aspects of linguistic expression. When exploring the relationship between gesture imitation and linguistic interpretation, the distinction between meaningful and meaningless gestures deficits plays a crucial role. As some researchers pointed out (Tessari & Rumiati 2004, Tessari et al., 2007) one of the most commonly-used and widely-accepted tests for Ideo-Motor apraxia (De Renzi et al., 1968) does not allow assessment of an isolated deficit for meaningful (or, vice versa, meaningless) gestures because in this test meaningful and meaningless gestures are mixed together. According to the authors, this mixed condition impedes the triggering of the stored semantic meaning of meaningful gestures and the processing of these gestures through the semantic route. When meaningless and meaningful gestures are presented in a mixed condition, participants imitate both types of gestures through the visuo-motor route, following the economy principle that “less (cognitive resources) is more (efficiency)”. A similar phenomenon can be seen in linguistic models for words and non-words that are read aloud (Coltheart et al., 1993). When meaningful and meaningless gestures are presented in separated blocks, however, the two routes are selectively activated; it is thus possible to see dissociated performance. Consistent with this view, Tessari and colleagues (2007) illustrated that imitation performance of meaningful and meaningless gestures may be selectively impaired in patients with unilateral (left or right) brain damage only when presented in separated blocks. Double *Classical* dissociations were detected in both directions, supporting a functional segregation between these two types of gestures. In the mixed presentation, when imitating meaningful as compared to meaningless gestures, none of the patients presented a dissociated performance. Prompted by these results, further research investigated possible overlapping between processing of meaningful gestures via the semantic route, and of retrieval of word meaning via the lexical-semantic route. Mengotti and colleagues (2013) investigated performance on two separate imitation tasks involving imitation of meaningless or meaningful gestures as a function of the degree of linguistic deficit defined by performance on three subtests (comprehension, naming, repetition) of an aphasia battery (Italian version of the Aachen Aphasia Test [AAT]; Luzzatti et al., 1996). At the single-case level, selective, isolated impairment in linguistic measures (Picture Naming, Repetition and Comprehension subtests of AAT) and gesture imitation were detected, suggesting that these abilities rely upon distinct cognitive functions. However, significant correlations were detected between Picture Naming and Repetition subtests of the AAT and the imitation of meaningful gestures, whereas performance on meaningless gestures imitation significantly correlated with performance on the Comprehension subtest of the AAT. Lesion analysis revealed that different portions of the inferior temporal lobe, such as the dorsal part of the angular gyrus and the ventral/anterior portion of the supramarginal gyrus, are selectively involved in the imitation of meaningless and meaningful gestures, respectively. Moreover, the same neural lesions associated with meaningful gesture impairment (but not meaningless gesture impairment) were also associated with poor performance on Picture Naming and Repetition subtests. The authors concluded that, even if cognitive mechanisms underlying imitation of meaningful gestures and linguistic lexical-semantic access may be selectively impaired and, thus, considered as independent processes, brain networks can partially overlap. Similar results were subsequently obtained by Achilles and colleagues (2016), who compared both left and right hemisphere stroke patients in a gesture imitation task, distinguishing between meaningful and meaningless gesture performance. The severity of apraxia, measured as the degree of impairment in imitating gestures (either meaningful or meaningless) significantly predicted poor performance on meaningless, as compared to meaningful, gestures. The presence of aphasia (especially at a mild or severe level), instead, significantly predicted the degree of imitating deficits for meaningful gestures only. In another study that led to similar conclusions (Xu et al., 2009), an fMRI investigation on healthy participants detected overlapping activation patterns for observation of symbolic gestures pictures and vocal auditory matched stimuli. Specifically, both types of stimuli activated bilateral modality-specific areas in superior and inferior temporal cortices. In explaining their findings, the authors claimed that there could be a shared cognitive mechanism between spoken language and meaningful gestures execution which extracts salient features from both vocal-auditory and gestural-visual stimuli. In this view, language and meaningful gestures may share an evolutionary origin for human communication, and the mechanism they share may enable the linking of a gesture or a sound with its meaning, in order to support either gestural or spoken communication.

1.2.3 Apraxia and Language interaction in Broca's area

Broca's area has been associated with a variety of cognitive functions, such as speech production (Dronkers, 1996; Watkins & Paus, 2004; Papoutsi et al., 2009), language comprehension (Friederici, 1997; Chee et al., 1999; Embick et al., 2000; Fadiga et al., 2002; Wilson et al., 2004) and music processing (Maess et al., 2001; Koelsch, 2006; Fadiga et al., 2009). A large number of neuroimaging studies have shown that Broca's area is activated during action-related tasks, such as the observation and imitation of finger movements (Iacoboni et al., 1999), the observation of meaningful versus meaningless actions (Decety et al., 1997), the observation of pictures displaying an action as compared to pictures without an action (Hamzei et al., 2003) and action imitation (Chaminade et al., 2002). Binkofski & Buccino (2004) reviewed results of these studies and proposed that Broca's area constitutes a high level sensorimotor interface integrating sensory stimuli and cognitive tasks with the related motor representations of hand-related actions. Pazzaglia et al. (2008) revealed that apraxic patients with gesture production deficits, compared to non-apraxic patients, were not able to judge the correctness of the execution of meaningful (transitive or intransitive) gestures. In apraxic patients, both frontal and parietal lesions were detected, indicating a role of both areas in performing gestures, but poor performance in the gesture recognition task was specifically associated with damage to the opercular and triangular portions of the inferior frontal gyrus. Interestingly, the authors explained the lack of a parietal involvement in gesture recognition, previously highlighted by other studies (Heilman et al., 1982; Rothi & Heilman, 1985; Buxbaum et al., 2005), as a function of the specific characteristics of the task employed in their study, relative to other tasks used in previous studies. The task used by Pazzaglia et al. assessed the ability to judge whether the ultimate goal of transitive gestures was satisfied or whether the symbolic meaning of intransitive gestures is maintained, while the kinematic–proprioceptive features and the general plan of action were maintained even in the incorrect gestures. Thus, according to the authors, activations in the left inferior frontal gyrus could evidence access to the meaning of the performed gesture. Fazio and colleagues (2009) conducted a lesion analysis in left frontal damaged aphasic patients who were tested in an extensive neuropsychological battery, which included two experimental tasks that entailed putting pictures depicting action execution by humans (e.g. a person grasping a bottle of water) versus physical events (e.g. falling down of a bicycle) into the correct sequence. Results showed that aphasic patients with Broca's lesions and without apraxic deficits were specifically impaired in sequencing pictures representing human actions, albeit not physical events. According to the authors, Broca's region could subserve a general computational mechanism, shared by multiple domains, enabling to organize and comprehend hierarchically compositions of elements. With respect to actions, Broca's lesion should impede comprehension of the hierarchical composition of motor acts, in agreement with Grafton & Hamilton (2007). A recent study with combined behavioral and voxel-based lesion symptom mapping analysis in 50 left brain damaged patients (Weiss et al., 2016) explored the relationship between praxis tasks (pantomime on presentation of object pictures and imitation of meaningful and meaningless gestures) and neurolinguistic measures (naming, reading, writing and auditory comprehension). Behavioral data showed significant correlations between almost all linguistic and praxis measures, with a lack of significance only between writing and imitation of meaningless gestures performance and between a language compound domain score and performance on imitation of meaningless gestures. Lesion analyses for combined aphasic and apraxic deficits demonstrated that patients with both aphasia and apraxia had common lesions encompassing the left inferior frontal gyrus (IFG) and, in particular, in the connectivity-based anterior-ventral sub-area of Broca's area (Brodmann area 44). In a functional-neuroanatomical study on Broca's area subdivision and characterization (Clos et al., 2013), this anterior-ventral sub-area was enclosed in a cluster thereby subserving our ability to extract meaning from sensory information and semantic processing. Specifically, this cluster is strongly associated with various key aspects of language processing (e.g. semantics, syntax, phonology and overt as well as covert speech) and is significantly more involved than other clusters in social cognition tasks. Clos and colleagues argued that this association may reflect an access to semantics in the form of previously acquired (verbal and non-verbal) conceptual knowledge that is required in the language domain but also in social interactions when we need to recognize meaningful cues in other people's behavior, gestures and mimicry. In agreement with this hypothesis, according to Weiss and colleagues (2016), common lesions for apraxic and aphasic patients in this anterior-ventral sub-region of Broca’s area correspond to an overlapping substrate for processing of meaningful actions and of language.

1.2.4 Apraxia and Action-related linguistic tasks

According to an embodied perspective of cognition (Barsalou et al., 2003), conceptual knowledge is based on our direct sensory and motor experience with the external world, and is rooted in brain areas that are responsible for perception and motion. When we need to retrieve the conceptual content that a word or sentence describes, we need the simulation (i.e. the building of an internally generated representation) of that word or sentence, which involves the same sensorimotor neural correlates as during execution of an action or interaction with an object. In a study conducted by Zwaan et al. (2004), healthy participants were presented with auditory sentences describing the motion of a ball toward or away from the observer and were then asked to judge whether two sequentially presented pictures of the ball (separated by a mask) were the same. The two pictures of the ball could suggest a movement away from the observer (the first ball was slightly larger than the second) or a movement toward the observer (the first ball was smaller than the second). This movement may or may not have matched the action described. Results showed that participants were faster when the picture sequence matched the movement described by the sentence, suggesting that sentence comprehension involves the perceptual simulation of the event described in a sentence. Thus, a considerable number of neuroimaging studies explored the association between activations in the sensory and motor system and performance on several language and conceptual tasks (see Pulvermüller, 2005; Watson et al., 2013; Pazzaglia, 2013 for extensive reviews). For example, Hauk et al. (2004) found that the activity in the premotor and primary motor cortex was modulated in a somatotopic manner when participants passively read action words performed with different body parts (e.g. "pick", "lick", "kick"). Tettamanti et al. (2005) demonstrated that listening to action-related sentences activated a left fronto-parieto-temporal network that included the inferior frontal gyrus (IFG), the premotor cortex, the inferior parietal lobule (IPL), the intraparietal sulcus, and the posterior middle temporal gyrus. These regions were identified as a putative homologue of the monkey mirror system that enables action execution (Rizzolatti & Matelli, 2003; Rizzolatti & Craighero, 2004) and is activated during observation of actions performed by others (Fadiga et al., 1995; Iacoboni et al., 1999; Buccino et al., 2001 and 2004a; Fadiga et al., 2002). Thus, data provided by Tettamanti and colleagues (2005), suggest that listening to action-related sentences engages the same neural networks responsible for action execution and observation, and that this activation reflects retrieval of action-knowledge, stored within these systems, during linguistic tasks. An fMRI study on healthy participants detected significantly greater activation in the MT+ visual motor area for motion sentences comprehension than for two other types of sentences (static sentences or fictive sentences), indicating that listening to action-related sentences recruits those neural processes that are responsible for visual perception of motion (Saygin et al., 2010). Sakreida et al., (2013) investigated the role of primary sensory and motor areas in healthy participants when asked to judge the familiarity of a noun-verb couple. The verb/noun couples could contain nouns referring to graspable/non-graspable objects and motor/non-motor verbs. This enabled mapping of each noun/verb couple onto a concrete/abstract axis to explore selective brain activations associated with concrete vs. abstract words. Results detected broad activations in the left primary and secondary motor cortices, including lateral motor/premotor cortex and supplementary motor area, in agreement with the embodied perspective on the crucial role of motor areas in language processing. Moreover, contrast in concrete vs. abstract pairs revealed specific activations for concrete words in the inferior frontal gyrus. In agreement with this view, patients with aphasia (Saygin et al., 2004) showed poor performance in matching both pictures of pantomimes with their corresponding object (non-linguistic action comprehension task) and in matching an incomplete transitive sentence with the corresponding missing object (linguistic action comprehension task). Defective performance in the pantomime-matching task was associated with lesions in the left inferior frontal premotor and motor cortex, highlighting a shared neural network between action execution and action understanding. Although no overall correlation was detected between patients' deficits in the two tasks, and despite the association of distinct lesion patterns with the pantomimes and the verbal matching tasks, a large cluster of patients with relatively mild and relatively fluent aphasia showed correlated impaired performance in the two tasks. Moreover, lesions associated with linguistic sentences matching encompassed a region in the anterior inferior parietal lobe, which was found to be part of the human mirror neuron system and supposed to be involved in actions understanding (Buccino et al., 2004a). The authors concluded that impairments in both linguistic and non-linguistic action understanding may be supported by the same mirror-neuron system involved in action execution. Coherently with this view, a study on left hemisphere brain injury patients with or without limb and/or buccofacial apraxia, compared to patients without apraxia, investigated the ability to match sounds evoking human-related actions or nonhuman action sounds with specific visual pictures (Pazzaglia et al., 2008). Action-related sounds could be referred to hand or mouth movements. Results showed that performance on hand and mouth sound-to-picture matching tasks was selectively affected in limb and buccofacial apraxia patients, respectively. Moreover, a recent study (Desai et al 2015) showed that, when controlling for grammatical class in left hemisphere lesioned patients, motor performance in a reaching task was more correlated with processing of action-related words (both action verbs and object nouns) relative to non-action-related words. Greater impairment in the reaching task significantly predicted performance in action relative to processing of abstract words at both implicit (lexical decision task) and explicit levels (semantic similarity matching task). Thus, this study illustrates that stroke patients' performance in a reaching motor task is selectively predictive of semantic processing of action concepts. However, other studies reported evidence in contrast with the hypothesis that motor simulation is required to retrieve action information in linguistic tasks and that the motor system represents the neural substrate of action knowledge (e.g. action recognition, action-related words comprehension). Two Transcranial Magnetic Stimulation (TMS) studies investigated the role of the primary motor cortex during action-verbs processing, showing that enhanced activity in the primary motor cortex responsible for hand movement was modulated by hand-action-related verbs only when measured at 500 ms post-stimulus (Papeo et al., 2009) and when hand-action-related verbs were presented in first person (i.e. when the self was recruited as agent; Papeo et al., 2011). According to the authors, these findings indicate that the primary motor cortex is involved in post-conceptual processing (i.e. after the retrieval of motor representations) rather than in lexical-semantic action retrieval. Weiss et al. (2016) demonstrated that the severity of apraxia (as indicated by performance in various gesture execution tasks) significantly correlated with lesions in the motor and premotor areas, whereas performance in action-related language was not associated with neural activity in motor or premotor regions. Negri et al. (2007b) demonstrated that in left hemisphere stroke patients, at single-case level, performance on action-related linguistic tasks (object naming and pantomime naming) and on their corresponding action execution tasks (object use and pantomime imitation tasks) could double dissociate. Specifically, the authors reported on one hand, a number of cases where patients were able to use objects despite being impaired at recognizing the associated pantomime and patients who were able to use objects but had impaired performance in the object recognition task. On the other hand, they observed several cases in which patients were impaired for pantomime imitation but still able to recognize them when performed by others, and others who were impaired in using objects despite being spared in object recognition. Similar results were subsequently reported by two other studies in left hemisphere stroke patients conducted by the same group (Papeo et al., 2010; Papeo & Rumiati, 2013). Double dissociations were observed between the ability to use tools and the ability to match the corresponding tool picture with the tool noun, as well as between the ability to imitate pantomimes and the ability to produce (when presenting a pantomime picture) the corresponding action verbs or the ability to match the pantomime picture to the corresponding verb (Papeo et al., 2010). Furthermore, the ability to execute intransitive familiar gestures was found to double dissociate from both the ability to retrieve (naming task) and to recognize (word-to-picture matching task) the corresponding word of the gesture (Papeo & Rumiati, 2013). Neuroimaging studies with fMRI on healthy participants explored the interaction between language and action when different kinds of verbs (Rüschemeyer et al., 2007) or different contexts in which a verb was presented (i.e. positive vs. negative, Tomasino et al., 2010) were taken into account. Rüschemeyer et al. (2007) investigated neural correlates when healthy participants viewed (and covertly read on a screen) verbs describing motor actions (e.g. "greifen", which means "to grasp") as compared to verbs describing abstract actions (e.g. "denken", which means "to think") and when participants viewed morphologically complex abstract verbs with motor stems (e.g. "begreifen", which means "to comprehend" but contains the motor stem "greif") compared to morphologically complex abstract verbs without motor stems (e.g. "bedenken", which means "to consider" and contains the non-motor stem "denken"). Results showed greater activation in the sensorimotor and secondary somatosensory cortex for simple concrete motor verbs as compared to abstract verbs, but not for morphologically complex abstract verbs with motor stems as compared to morphologically abstract verbs without. Instead, morphologically complex verbs with motor stems correlated with right lateral temporo-occipital junction area. Tomasino et al. (2010) investigated whether positive (e.g. *scrivi!*, "do write!") or negative (e.g. *non scrivere!*, "don't write!") hand-action-related imperative verbs could modulate neural activations in the sub-regions of primary motor and premotor cortices subserving hand-movement representations. Results showed that neural activity in these two key areas was significantly lower, in both hemispheres, for negative imperatives compared to positive imperatives. To sum up, recent studies have suggested that neural regions associated with action-related linguistic performance may not coincide with mirror neuron systems responsible for action execution (Papeo et al., 2009; Papeo et al., 2011; Weiss et al., 2016). Patients' performance on motor tasks may correlate with action-related linguistic performance (Pazzaglia et al., 2008; Desai et al., 2015), but there is also evidence that these two domains dissociate (Negri et al., 2007b; Papeo et al., 2010; Papeo & Rumiati, 2013). Furthermore, functional activation in the mirror system and in motor areas during a variety of linguistic tasks can be determined by contextual factors, such as when the verb is presented in a negative vs. positive imperative form (Tomasino et al., 2010) or in first vs. third person (Papeo et al., 2011) and when participants are required to covertly read simple verbs vs. morphologically complex verbs (Rüschemeyer et al., 2007).

1.2.5 Summary and unsolved questions

In literature, it is well known that aphasia and apraxia often co-occur after left hemisphere lesions. While some researchers argued that this tight relationship is due to anatomical proximity of linguistic and praxis domains, which can be easily damaged after infarction of the left hemisphere, other authors suggested that these two abilities may share common functional mechanisms and, thus, the same neural pathways. For example, recent studies showed that deficits in the imitation of meaningful gestures, but not of meaningless gestures, significantly correlated with poor performance on linguistic tasks (Mengotti et al., 2013; Achilles et al., 2016). The shared mechanism that is common to meaningful gestures imitation and linguistic performance may be the access to semantic knowledge. Furthermore, a large amount of studies within the embodied theoretical framework (Hauk et al., 2004, Tettamanti et al., 2005; Saygin et al., 2010; Sakreida et al., 2013) showed that action words/sentences processing activates the same brain areas that are activated during gestures observation and imitation. These results led the authors to claim that the common mechanism shared by language and praxis domains is the motor simulation of action. This simulation is supposed to happen when we observe, imitate or understand an action performed by another person, but also when we try to understand the meaning of a word/sentence related to an action. Even though the role of motor simulation in action words and sentence processing has been questioned (Negri et al., 2007b, Papeo et al., 2009, 2010; Papeo & Rumiati, 2013; Weiss et al., 2016), a large amount of research has highlighted a strict link between gesture execution and action word processing. The relationship between gestures execution and action language processing was explored in the first study through the assessment of action verb production and comprehension, semantic knowledge (including the evaluation of action knowledge) and gesture production tasks. Taking into account the dual-routes model, gesture production tasks included both meaningless and meaningful gestures. Following the dual-routes models predictions, we expect a strict relationship between meaningful, but not meaningless, gestures and performance on verb production and comprehension tasks and/or performance on tasks evaluating semantic knowledge.

1.3 TOOL KNOWLEDGE AS AN INTERFACE BETWEEN PRAXIS AND SEMANTICS

1.3.1 The organization of Tool knowledge in the Semantic System

When we interact with a tool, information derived from our experience with it - such as how it is used, for which purpose, in which context -should be integrated in order to use it properly and to realize goal-directed actions. This means that perception, action and cognition are strictly linked in determining tool conceptual knowledge. Different theories regarding semantic memory make distinct predictions about the way in which tool knowledge is represented in the brain (for a recent review on the various theoretical account, see Mahon & Hickok, 2016). According to the embodied theory of cognition, tool knowledge is embodied in the sensory and motor systems (Barsalou et al., 2003). The salient features of an object - its shape and color, how it moves, how it is used, and our affective response to it- contribute to build the semantic concept of that particular object (Allport, 1985; Damasio, 1990; Barsalou et al., 2003; Martin, 2007). Each of these salient features is processed by a modality-specific neural source, e.g. sensory (visual, auditory, tactile, olfactory, gustatory), motor, linguistic or affective source of information. In accordance with this view, many fMRI studies on healthy participants showed that a complex left lateralized network of areas, including left posterior middle temporal, left inferior parietal and premotor areas – and, in particular, the ventral premotor cortex -, was active when participants viewed or named tools to a greater degree than when they processed other kinds of objects (Chao, Haxby, & Martin, 1999; Chao & Martin, 2000; Creem-Regehr & Lee, 2005; Mahon et al., 2007), and during the performance of tasks requiring association of manipulable tools on the basis of their action or their functional properties (Kellenbach et al., 2003; Boronat et al., 2005; Canessa et al., 2008). According to the strongest version of the embodiment perspective, action plays a privileged role in conceptual knowledge of tools. According to this perspective, when we need to retrieve some kind of knowledge about a manipulable tool, we need a mental simulation or imaging of that tool and the situations in which we interact with it. This means that we need to re-activate those neural systems – e.g. premotor and motor areas- that were engaged when we used that tool. When these neural areas are damaged, any mental simulation or imaging of an action with the tool, as well as of the tool itself, is impaired (Gallese & Lakoff, 2005). Conversely, according to another perspective from the embodiment framework (van Elk et al., 2014; Martin, 2016), conceptual tool knowledge is not represented in primary sensory and motor areas. The salient features of tools, processed by modality-specific sensory and motor areas, are combined together in multi-modal convergence areas, building multi-modal representations of tools. Numerous neuroimaging studies, predominantly fMRI investigations, have suggested that the left posterior middle temporal gyrus (pMTG) is a multi-modal convergence zone that is critical for tool representation (Beauchamp et al., 2002; Devlin et al., 2002; Mahon et al., 2007; Beauchamp & Martin, 2007; Campanella et al., 2010). A recent fMRI study (Fernandino et al., 2015) investigated the neural activations related to words referred to modality-specific tool properties (i.e. color, visual shape, visual motion, sound, manipulation) during a semantic decision task. Results showed that tool sensory-motor attributes modulated activations in secondary sensory areas and in multimodal integration areas rather than in primary sensory and motor areas. Furthermore, data revealed a hierarchical system of multiple converging sensory and motor pathways underlying the representation of word meaning, which included several regions implicated in multisensory integration, such as the left pMTG and the left angular gyrus. Because of its intensive neural connectivity with visual motor areas (e.g. area MT for movement perception) and inferior parietal areas (assumed to be crucial for praxis and gestures execution, [Buxbaum et al., 2003; Buxbaum et al., 2005; Buxbaum et al., 2007]), the pMTG may be responsible for the integration of praxis information on tool-related actions with other types of tool semantic knowledge (Beauchamp & Martin, 2007; Kalénine et al., 2010; Kalénine & Buxbaum, 2016). Another theoretical perspective, namely “the hub-and-spokes theory”, claims that, in addition to modality-specific cortices (the “spokes”), which process specific features of objects, there is a cross-modal interaction zone (the “hub”), located bilaterally in the anterior temporal lobes, in which all modality-specific types of information converge. As in the embodiment theories, the spokes can be selectively damaged, resulting in modality-specific deficits. In contrast to the embodiment theories, however, here object knowledge is represented in the anterior temporal lobes in an amodal, rather than multi-modal, way. This means that when the hub is damaged, the semantic deficit involves any semantic category and any sensory, linguistic or motor modality. Consistent with this hypothesis, when inhibitory repetitive Transcranial Magnetic Stimulation (rTMS) was applied to the hub, participants exhibited significantly lower performance in naming objects, regardless of their category (e.g. both tools and animals), whereas when inhibitory rTMS was applied to a left inferior parietal area, participants showed a category-specific deficit for manipulable tools only (Pobric et al., 2010). Similarly, another study on healthy volunteers (Ishibashi et al., 2011) showed that inhibitory rTMS applied to the left inferior parietal lobule caused a lower performance in matching tools that shared the same manipulation, but not in matching tools that shared the same function, while inhibitory rTMS applied to the left anterior temporal lobe provoked slower performance for both manipulation and function judgments.

1.3.2 Tool knowledge and Apraxia: the ventral and the dorsal streams

Different lines of research have indicated that there is an interaction between those systems devoted to object identification and those required to correctly manipulate tools. According to a cognitive neuroanatomic framework (Goodale & Milner, 1992; Milner & Goodale 1995; Ungerleider and Mishkin, 1982), there is a distinction within the visual system between a neural path devoted to object recognition (the “ventral” visual processing stream) and a neural path devoted to process object-directed actions (the “dorsal” visual processing stream). Two key areas - the left inferior parietal lobule (IPL) and the bilateral occipito-temporal cortex- play distinct crucial roles in the dorsal and the ventral visual streams, respectively. Patients with damage to the left IPL were unable to make accurate reaching movements towards a visual target, although they could accurately perceive the target (Damasio & Benton, 1979, Perenin et al., 1988). Conversely, patients with bilateral lesions of the lateral occipito-temporal cortex were impaired in recognizing objects but were still able to grasp and make reaching movements toward the same objects (Goodale et al., 1991; Milner et al., 1991). Recently, it has been proposed that a further functional and neuroanatomical subdivision in the dorsal stream exists. Rizzolatti & Matelli (2003) proposed that parieto-frontal circuits are organized in a dorso-dorsal pathway (running from the visual association area V3 to the visual area V6 and the mesial part of the intraparietal area in the superior parietal lobule (SPL) and from here to the dorsal premotor cortex (dPMC)) and a ventro-dorsal pathway (running from medial superior temporal areas to the inferior parietal lobule (IPL), and from here to the ventral premotor cortex (vPMC)). This neural segregation reflects a functional dissociation between the two streams, so that lesions to the SPL and the IPL lead to distinct neuropsychological deficits. According to the authors, the dorso-dorsal pathway is devoted to the ‘online’ control of actions (a visual control of the ongoing action); damage to this pathway, in particular to SPL, results in optic ataxia. The ventro–dorsal pathway supports different processes, such as space perception, action planning and the recognition of actions executed by other people. In fact, the IPL plays a role in space perception and object awareness: lesions to the lower part of the right IPL cause neglect. Furthermore, the ventro-dorsal stream transforms visual object features (such as size and shape) into the appropriate motor schema, supporting action planning and object grasping and manipulation. In fact, lesions to the rostral part of the left IPL cause Ideo-Motor apraxia. Binkofski & Buxbaum (2013) expanded upon these findings, and proposed that the dorso-dorsal pathway is an immediate, visual route to action which processes the structural characteristics of objects in the peripersonal space (e.g., shape, size, and orientation) to “Grasp” them. Consistent with this view, previous studies suggested that, when applying TMS to the anterior part of the intraparietal sulcus (IPS), virtual lesions provoked a deficit in goal-directed prehensile actions (Tunik et al., 2005): as compared to patients with parietal lesions sparing this area, patients with lesions to the anterior part of the IPS had selective deficits in object grasping, but not in object reaching. Moreover, in an fMRI study, the anterior part of the IPS was active when healthy participants made grasping movements toward objects (Binkofski et al., 1998). In contrast, the ventro-dorsal stream subserves action planning and action processing by accessing long-term object-use representations (Binkofski & Buxbaum, 2013). Lesions of the ventro-dorsal stream produce an impairment to the “Use” system, causing difficulties in all those tasks that require knowledge of skilled object use, such as pantomime of object use, actual tool use and action recognition. According to the authors (Binkofski & Buxbaum, 2013), both the “Grasp” and the “Use” systems are engaged and coordinated when we need to perform typical everyday actions and perhaps reaching movements to objects. Evidence of specific contributions of the dorso-dorsal, ventro-dorsal and ventral streams in different types of action and gesture tasks emerged from recent studies on left hemisphere stroke patients with apraxia. Using the Voxel-Based Lesion-Symptom Mapping (VBLSM) technique, Hoeren and colleagues (2014) investigated the neural correlates of imitation of meaningless gestures and pantomime execution (after presentation of a picture of a tool), making distinctions between “content errors” (production of semantic-related actions) and “movement errors” (overall correct but clumsy actions, hand configuration or orientation errors). Results showed that imitation of meaningless gestures involved areas enclosed in the dorso-dorsal stream, such as the left lateral occipito-temporal cortex, the left SPL and the left posterior IPS, whereas pantomime engaged both areas of the ventro-dorsal (e.g. the anterior part of the IPL and the pMTG) and of the dorso-dorsal (e.g. the lateral occipito-temporal cortex, the left posterior IPS and SPL) streams as well as white matter that was part of the ventral stream (extreme capsule and insular white matter). Furthermore, content errors, which indicated an inability to associate tools with their corresponding actions, were significantly associated with IPL lesions, assumed to contain stored knowledge about skilled-actions (Heilman et al., 1982; Buxbaum et al., 2007), and with anterior temporal regions, that are part of the ventral stream for object identification and object semantics (Patterson et al., 2007; Pobric et al., 2010; Ishibashi et al., 2011). Another MRI study on left hemisphere stroke patients (Martin et al., 2016) investigated neural underpinnings of tool use and neural activation correlated with a tool-object (e.g. hammer and nail) matching task. Results showed that both tool-object matching and tool use deficits were significantly related to lesions within the left IPL and other areas of the ventro-dorsal stream. However, poor performance in the tool-object matching task, relative to tool use, also involved the anterior temporal lobe and regions of the ventral stream. Overall, these studies suggested that different streams for praxis and object semantics highly interact when we need to use tools in a purposeful manner.

1.3.3 Tool knowledge and Tool Use: Action semantics

A large number of studies in the literature suggest that our ability to use tools is supported not only by those neural systems that are responsible for action planning and motor control, but also by some kind of semantic knowledge about tools, which may consist of multimodal (Martin, 2016) or amodal (Patterson et al., 2007) knowledge, derived from different types of modality-specific information on objects. Recently, these abilities have been combined under the name "action semantics" (van Elk et al., 2014) to emphasize the fact that action and conceptual knowledge are strongly interlinked in determining our ability to use tools. The association between tool use and tool semantic knowledge has been widely studied in neurodegenerative patients with predominant semantic deficits, such as in patients with Semantic Dementia (SD). Steinthal (1871) was the first to use the term "apraxia" when describing an aphasic patient with defective performance in using tools, claiming that this deficit was an obvious amplification of aphasia. Similarly, some studies have evidenced a relationship between semantic decline and the ability to use tools in SD patients (Hodges et al., 2000; Bozeat et al, 2002; Coccia et al., 2004). For example, SD patients were reported to be severely impaired in semantic tasks requiring matching or naming of objects and in demonstrating the use of the same objects (Hodges et al., 2000). Moreover, the degree of the semantic deficit significantly correlated with the severity of object use performance. A subsequent study (Bozeat et al., 2002) expanded upon these results, demonstrating that relatively spared performance in semantic tasks positively correlated with residual abilities in demonstrating the use of a tool. Furthermore, tool use performance in SD patients improved when the tool was presented with its corresponding recipient object (e.g. using a screwdriver with a screw). The authors claimed that having not only the target object but also its natural recipient might improve patients' use of the object for two reasons. First, the recipient object may provide contextual information about the situation in which the object can be used and, therefore, give access to further conceptual knowledge of the object. Second, the presence of a recipient object provides a clue as to the function of the object and the ultimate goal of the action, triggering a trial-and-error problem-solving approach in the patient. Despite these results, dissociations between deficits in conceptual object knowledge and the ability to use tools were also reported. Negri and colleagues (2007a) described two patients, one with SD and the other with atypical onset of Alzheimer's disease and predominant lexical-semantic deficits, who were significantly impaired in tasks tapping verbal and non-verbal semantic knowledge about objects (e.g. knowledge about function) but who had a significantly better performance on object use tasks. According to the authors, tool semantic and tool use abilities decline independently and may be represented separately in the brain. Longitudinal studies (Coccia et al., 2004; Silveri & Ciccarelli, 2009) supported this hypothesis and demonstrated that semantic knowledge and tool use abilities declined independently in SD patients, so that a patient with mild semantic deficits still had a spared performance in demonstrating the use of a tool. However, as revealed by follow-up investigations, after approximatively 2 (Silveri & Ciccarelli, 2009) and 4 (Coccia et al., 2004) years, as the semantic deficit became severe, tool use abilities progressively decayed as well. Furthermore, the relatively spared ability to use tools in the early stage of the disease improved patients' naming abilities (Coccia et al., 2004). According to Coccia and colleagues (2004), a spared performance in using tools at the early stages of the semantic impairment could be explained by preserved praxis processes, supported by the dorsal stream. However, the resulting parallel decline in both tool use and tool knowledge suggest an impairment to a unitary semantic system, composed of dynamic semantic representations, which can be activated differently depending on the modality and the context. Similarly, according to Silveri and Ciccarelli (2009), semantic knowledge, and especially knowledge about functional aspects of objects, is necessary to accurately use tools, but a non-semantic mechanism may compensate for semantic loss at the early stage of disease. In accordance with the hypothesis that tool semantic knowledge is necessary to correctly illustrate the use of a tool, a recent study (Baumard et al., 2016) revealed that SD patients had impaired performance both in associating objects with shared functional/contextual features and also in demonstrating the typical gesture associated with a tool, either in absence of the tool (pantomime) or with the tool in hand (single tool use). Specifically, the authors argued that loss of tool semantic knowledge was responsible for the inability to imagine the absent tool (e.g. a hammer) or to access which action can be performed with a tool (e.g. access the gesture that is made with a hammer). Interestingly, however, patients had spared ability to use a tool (i.e. the hammer) when the corresponding recipient object was presented (e.g. the hammer and the nail are presented together). Thus, according to the authors, semantic memory is not engaged in every task that entails tool use ability, but it is required when some stored knowledge about the tool (e.g. imagine the absent tool) is necessary to plan the proper action (i.e. during pantomime and single tool use). Indeed, residual tool application may be enabled by the existence of another mechanism (i.e. technical reasoning, see paragraph 1.3.4 for an extensive explanation), which is independent from semantic memory. The hypothesis advanced by this latter study was compatible with that proposed by some previous studies (Bozeat et al., 2002; Silveri & Ciccarelli, 2009) and appears to account, at least partially, for the discrepancies reported on tool use abilities in SD patients.

1.3.4 Manipulation-based approach versus Technical reasoning Hypothesis

In the embodied theoretical framework, it was proposed that human ability to use tools relies upon a multi-modal representation of tool knowledge, which encompasses sensory and proprioceptive features of tools, knowledge of tool function, and knowledge of the way in which a tool can be afforded and manipulated (van Elk et al., 2014). Among all these modality-specific features, knowledge of how to correctly afford and manipulate a tool seems to play a crucial role in determining tool use deficits. Manipulation knowledge (also called “stable affordance” [Borghi et al., 2004] or “object affordance for conventional use of familiar tools” [Buxbaum & Kalénine, 2010]) can be defined as stored knowledge about the specific gesture associated with a familiar tool. A deficit in accurate use of tools is one of the core features of Ideational Apraxia (Liepmann, 1908; De Renzi et al., 1968; De Renzi & Lucchelli, 1988), which causes a deficit in ideating and programming a complex action (Liepmann, 1908) but also in demonstrating the use of a single tool (De Renzi et al., 1968). According to the manipulation-based approach, damage to manipulation knowledge, represented within the ventro-dorsal stream, causes defective performance in all the tasks that require retrieval of information about tool-related actions, such as actual tool use, action recognition and pantomime execution (Binkofski & Buxbaum, 2013). Numerous neuropsychological and neuroimaging studies on both healthy participants and left hemisphere stroke patients showed results in line with the manipulation-based approach. Buxbaum & Saffran (2002) demonstrated that patients with apraxia and single tool use deficits, relative to non-apraxic patients, performed significantly worse in identifying the two objects that shared the same manipulation among three object pictures. Patients without apraxia, instead, were relatively spared in the manipulation task, but significantly more impaired in associating pictures of objects sharing the same function. Combined behavioral and lesion-based analyses in left hemisphere stroke patients showed that damage to the pMTG was correlated with semantic errors in a gesture recognition task (e.g. choosing the video corresponding to “sawing” instead of “hammering”, Kalénine et al., 2010) and also with poor performance in a conceptual task requiring association of objects that may be used together for a purposeful action (e.g. axe-wood, Kalénine & Buxbaum, 2016). According to the authors, the pMTG may store manipulation knowledge that is required both in conceptual and in gesture production tasks. Neuroimaging studies with fMRI on healthy participants demonstrated that a large left hemisphere network enclosing areas that are usually damaged in patients with apraxia, such as the premotor cortex, the pMTG and the IPL, was active during a semantic judgment task on pictures of objects sharing the same manipulation (Kellenbach et al., 2003; Boronat et al., 2005). Furthermore, a study with rTMS demonstrated that virtual lesions to the left IPL interfered with participants' ability to associate objects that could be manipulated in the same way (Ishibashi et al., 2011). However, recently the existence of manipulation knowledge has been questioned, with some authors claiming that manipulation or other types of semantic knowledge (i.e. functional knowledge) may not be crucial for actual tool use. According to the Technical reasoning hypothesis (Osiurak, 2014; Osiurak & Badets, 2016; for a similar view see also Goldenberg & Spatt, 2009; Goldenberg, 2014), we do not need to store knowledge about object use because we can reason about the physical and mechanical properties of an object (i.e. mechanical knowledge) to solve the problem of how that object can be used. Technical reasoning is the ability to identify correspondence between the physical properties of viewed tools and learned physical principles (mechanics, space, time, and effort). In this perspective, function knowledge is not used to access relevant information for object use, but to know where to get tools and objects that can be used in the intended action. Evidence of the existence of technical reasoning comes from studies on left hemisphere stroke patients who were selectively impaired in pantomiming the use of an object or in selecting the appropriate tool to lift a cylinder from a box among three unfamiliar tools presented to them (Goldenberg & Hagmann, 1998a). Only those patients who exhibited both pantomime and novel tool selection deficits also showed impaired performance in actual tool use. According to the authors, this result suggests that technical reasoning may compensate for the loss of knowledge about tool use (as demonstrated by pantomime deficits). Consistent with these results, tool use deficits have been reported in patients with Cortico-Basal Degeneration (CBD) who had spared semantic association abilities (Hodges et al. 1999). According to the technical reasoning hypothesis, tool use deficits in these patients may be due to elementary motor, sensitive and proprioceptive disorder rather than to loss of functional or contextual knowledge, as conceptual knowledge impairment is not part of the neuropsychological profile of CBD reported by Armstrong and colleagues (2013). To sum up, current literature on tool use disorders suggests that future research should further explore the role of manipulation and function knowledge versus technical reasoning in determining our ability to use tools.

1.3.5 Summary and unsolved questions

Tool use is the perfect example to understand how language, and particularly semantic knowledge about objects, and gesture execution interact. In fact, when we interact with an object, information derived from our experience with it - such as how it is used, for which purpose, in which context - should be integrated in order to use it properly and to realize goal-directed actions. To date, how semantic object knowledge is represented in the brain is still debated. According to the embodied perspective, object knowledge is embodied in those neural structures that are involved during object use, gesture execution, and action observation. However, a large body of evidence provided from patient studies showed that defective object use and degraded semantic knowledge can appear together, but also dissociate. Furthermore, neuroimaging findings demonstrated that the neural basis of tool use is dissociable from that of tool semantic knowledge, although these two systems highly interact. Thus, which type of semantic information is engaged during object use, and which is its relationship to general semantic memory has been an important issue in both the field of semantics and apraxia in recent years. Among all semantic features, manipulation knowledge (i.e. the specific gesture that can be done with an object) and function knowledge (i.e. knowledge about the purpose of an action with an object) seem to be relevant semantic features that can be accessed when we use an object. In the field of semantics, according to the multi-modal theories (Martin, 2016), object knowledge is derived from modality-specific cortices, widely distributed in the brain. However, there is a multi-modal convergence zone in the posterior part of the middle temporal gyrus (pMTG) that is crucial for tool use. In this area, various modality-specific types of information about objects, provided from the sensory-motor systems, are integrated together to support object use. According to another perspective, namely the Hub and Spokes theory (Patterson, 2007), relevant semantic knowledge for tool use is represented in modality-specific areas as well, but all types of modality-specific information are conveyed in a semantic hub, which is located bilaterally in the anterior temporal lobes. This means that a lesion to the anterior temporal lobes may disrupt specific information that is required during object use. In the field of apraxia, neuroimaging studies have identified a neural network, the ventro-dorsal stream, running from medial superior temporal areas to the inferior parietal lobule (IPL), and from here to the ventral premotor cortex (vPMC), which would process relevant semantic knowledge for tool use and support skilled actions. Thus, specific tool semantic knowledge that is retrieved when we execute tool-related gestures (e.g. manipulation knowledge) would be represented within this network. To understand the role of semantic memory in tool use, many studies focused on patients with Semantic Dementia, a neurodegenerative disorder associated with anterior temporal lobe atrophy, which cause a progressive decline in the ability to name, recognize and associate objects. In literature these patients are frequently reported as impaired in actual use of real objects, as well as in tasks that require knowledge about for what purpose and in which context an object can be used. Despite this, a prominent role of semantic memory in tool use has recently been questioned, while other cognitive mechanisms, such as technical reasoning, have been proposed as better candidates in affecting accurate object use (Osiurak, 2014; Baumard et al., 2016; Osiurak & Badets, 2016). Thus, one first issue that remains unsolved in literature is where specific semantic information about objects that can be related to action (i.e. function knowledge and manipulation knowledge) is represented in the brain, and which is the relationship with general semantic memory. This issue is the focus of the second study, which explored the neural basis of action semantics in patients with neurodegenerative diseases. Second, the role of semantic specific information in object use needs to be clarified. The third study of the present work aimed at shading light on this point.

1.4 WHAT IS ALREADY KNOWN, WHAT IS NOT: AIM OF THE THREE EXPERIMENTAL STUDIES

Aphasia and apraxia often co-occur in patients with left brain damage (de Ajuriaguerra et al., 1960; de Renzi et al., 1968; Papagno et al., 1993) and patients with neurodegenerative diseases have been reported to have poor performance in both tool use and semantic tasks (Baumard et al., 2016; Coccia et al., 2004; Hodges et al., 2000), but the reason why linguistic and praxis deficits are so tightly associated is still debated. Recent studies (Mengotti et al., 2013; Goldenberg & Randerath, 2015) showed that linguistic and praxis domains are, at least partially, supported by common neural substrates, but the interpretation of the interaction between language and praxis depends on which specific cognitive aspects are examined. Toward this direction, the first study focused on Ideomotor apraxia and its relationship with language deficits. Taking into account the theoretical models of apraxia, the study aimed at exploring whether different types of gestures (meaningful transitive, meaningful intransitive, meaningless) could be disproportionately impaired in patients with left hemisphere stroke and, since different types of gestures may be supported by distinct neural streams, whether performance on these gestures correlated, or not, with linguistic abilities. Furthermore, in literature few studies focused on the difference between meaningful transitive and intransitive gestures, and the interaction between the visuo-motor and the semantic route is debated (see paragraphs 1.1.4 and 1.1.5). The linguistic assessment included a standardized battery that was used in a previous study on the topic (Mengotti et al., 2013). Many studies demonstrated also that action word/sentence processing activated the same areas involved in gesture imitation (see paragraph 1.2.4). Thus, two tasks assessing action verb processing (comprehension and naming tasks) were also included in the linguistic assessment. Finally, patients were also tested with a semantic task evaluating different types of semantic association, including the ability to associate objects can be used together in the same action. We expect to find significant correlations between the ability to imitate meaningful gestures and performance on verb processing or semantic tasks, suggesting a strict link between action-related knowledge and praxis. The second study focused on object semantic knowledge, and in particular on the specific types of semantic information that are entangled under the name “action semantics” (i.e. the purpose of use of an object, its context of use, the way in which an object is manipulated). In literature, it is still debated whether these types of object knowledge related to action are represented in areas that are common with the motor system (Gallese & Lackoff, 2005), or in other specific brain areas and then join in a multi-modal convergence zone (Martin, 2016) or in a semantic hub (Patterson, 2007). This question is particularly important to understand the relationship between object semantics, action semantics and praxis, and to explain why praxis and semantic deficits are frequently correlated (for example in patients with Semantic Dementia), but may also dissociate (see paragraph 1.3.3). To this purpose, patients with various types of neurodegenerative diseases (including Semantic Dementia) were compared in a Category Decision task that explored the ability to associate objects on the basis of purpose, manipulation and context of use. We expect that manipulation knowledge may be selectively impaired, especially in those patients with ideomotor apraxia and visuo-constructional deficits. Furthermore, we aim to detect brain areas are associated with manipulation knowledge. According to the embodied framework, action knowledge is embodied in those primary sensory and motor areas that are responsible for action imitation, observation and execution (Gallese et al., 1996; Grèzes et al., 1998; Buccino et al., 2004b; Gallese & Lackoff, 2005). However, recent studies showed that left temporal and parietal areas that are part of the ventro-dorsal stream, and in particular the left posterior middle temporal gyrus, support manipulation knowledge that is required both in conceptual and in gesture production tasks (Kalénine et al., 2010; Buxbaum & Kalénine, 2016). We predict that manipulation knowledge, defined as information about the specific gesture that can be executed with an object, may be the semantic information that is engaged in praxis tasks and stored in left temporal and parietal areas that were reported in previous studies. Recent studies suggested that manipulation knowledge may be crucial in actual abject use (Borghi et al., 2004; Buxbaum & Kalénine, 2010; Binkofski & Buxbaum, 2013). This possible link between manipulation and object use was then explored in the third experiment. Patients with Alzheimer's

Disease were required to actually use objects and to associate pictures of objects according to manipulation or function. Two main theoretical perspectives are at odds in literature: the manipulation-based approach versus the technical reasoning hypothesis. In agreement with the manipulation-based approach, we expect that the ability to use tools would be related to manipulation knowledge. Furthermore, an intact function knowledge may support actual object use, when manipulation knowledge is damaged. To sum up, the three experiments reported in the present work provide new insights on the association between action semantic knowledge and praxis, in particular with respect to the execution of meaningful gestures, both intransitive or related to the use of objects.

CHAPTER 2. STUDY 1: ACTION SEMANTICS, GESTURAL SEMANTICS AND VISUO-MOTOR IMITATIVE PROCESSES. THE OVERLAP BETWEEN APHASIA AND APRAXIA IN LEFT HEMISPHERE STROKE

2.1 INTRODUCTION

According to the dual-routes models, the imitation of gestures is enabled by two distinct cognitive streams: a visuo-motor route, which allows the imitation of unknown, meaningless gestures that are performed by another person, and a semantic route, which is responsible for imitation of meaningful actions (Rothi et al., 1991; Cubelli et al., 2000). This distinction accounts for human ability to store memories about those gestures that have a meaning (e.g. waving the index finger to mean "no") so that we are able to easily recognize them, when performed by others, and execute them during everyday life. This is also true for transitive meaningful actions, such as actions that can be performed with objects and pantomime of object use. Rumiati & Tessari (2002) demonstrated that, for healthy individuals, meaningful actions (e.g. to brush one's own teeth) are easier to imitate than meaningless actions because we have stored long-term memories about these gestures. Thus, meaningful gestures can be quickly and easily retrieved as a whole when we access the action lexicon through the semantic route. Instead, meaningless, new gestures are processed more slowly, because the gesture has to be analyzed by the visual system and translated into a motor program. In addition, since meaningless gestures are not stored in long-term memory, they require a higher short-term memory load than meaningful gestures. Double dissociations in left brain damaged patients between performance on meaningless vs. meaningful gestures have been reported in literature, giving strong support to this model (Goldenberg & Hagmann, 1997; Bartolo et al., 2001; Tessari et al., 2007). Moreover, Positron Emission Tomography (PET) studies on healthy participants (Peigneux et al., 2004; Rumiati et al., 2005) and lesion analyses studies on stroke patients (Buxbaum et al., 2014), found distinct patterns of brain lesions associated with deficits in meaningful and meaningless gestures imitation. An interesting question in this framework is whether the presence of unimpaired non-lexical route may compensate the lexical route damage, allowing a patient with selective damage of the semantic route to imitate also meaningful gestures. Tessari & Rumiati (2004) demonstrated that, in healthy individuals, when meaningful and meaningless gestures are intermingled the semantic route is discouraged, and the non-lexical route is engaged in imitating both types of gesture. However, in the reported brain damaged patients with spared performance on meaningless gestures (Goldenberg & Hagmann, 1997; Bartolo et al., 2001), the intact non-lexical route did not compensate for meaningful gestures imitation, which remained severely impaired. Thus, the recruitment of the non-lexical visuo-motor route for all gestures, when the semantic lexical route is damaged, is still matter of debate. A further distinction in apraxia is between intransitive meaningful gestures (i.e. symbolic gestures) and transitive meaningful gestures (i.e. actual object use and pantomime of object use), which are supposed to rely upon distinct neural pathways as well (Bartolo et al., 2003; Buxbaum et al., 2014; Dressing et al., 2016). Buxbaum and colleagues (2007) demonstrated that left brain stroke patients with parietal lesions, involving in particular the left inferior parietal lobule, were more impaired on imitation of meaningful transitive actions (i.e. pantomime of object use) as opposite to meaningful intransitive gestures (e.g. signaling stop), whereas patients with corticobasal degeneration (CBD), and predominant fronto-parietal involvement, were equally impaired on both types of gesture. Furthermore, when considering the hand posture component of gestures, CBD patients were more impaired on meaningless than on meaningful gestures, whereas stroke patients showed the reverse pattern with predominant deficit of meaningful gestures. According to the authors (Buxbaum et al., 2007), these results suggest that CBD patients had an intact representation of meaningful gestures, as demonstrated by the meaningful superiority effect, which was previously described in healthy participants (Rumiati & Tessari, 2002). Conversely, the meaningful superiority effect was absent in left hemisphere stroke patients, who had defective performance on both types of gesture, but were significantly more impaired for the hand posture component of gestures when performing meaningful gestures. This result supports the hypothesis that stroke patients had damage of the long-term representations of known gestures, whereas CBD patients exhibited relative sparing of gestures meaning. Current research on apraxia have focused on which are the neural and cognitive bases underlying the execution and/or the imitation of different types of gesture (Buxbaum et al., 2014; Niessen et al., 2014; Hoeren et al., 2014; Vry et al., 2015; Dressing et al., 2016; Martin et al., 2016). Another important issue concerns the relationship between linguistic and praxis deficits, given the high frequency of coexisting aphasia and apraxia after left hemisphere stroke (de Ajuriaguerra et al., 1960; De Renzi et al., 1968; Papagno et al., 1993; Mengotti et al., 2013; Goldenberg & Randerath, 2015; Weiss et al., 2016) and of co-occurring semantic and tool use deficits in patients with semantic dementia (Hodges et al., 2000; Bozeat et al., 2002). In the field of the embodiment, many studies highlighted a strict relationship between mechanisms engaged in action production and in linguistic abilities (Hauk et al., 2004; Tettamanti et al., 2005; Pazzaglia et al., 2008; Sakreida et al., 2013; Desai et al., 2015). Other studies, instead, demonstrated that deficits in these two domains may dissociate (Negri et al., 2007b; Papeo et al., 2010; Papeo & Rumiati, 2013). Within the dual-routes model account, it was proposed that linguistic and praxis systems may tightly interact in tasks that require the retrieval of the meaning of actions and words. For example, recent studies demonstrated high correlations between imitation of meaningful gestures, but not meaningless, with performance on language repetition, naming (Mengotti et al., 2013), and comprehension tasks (Achilles et al., 2016). The aim of my first study consists in examining whether predictions of the dual-routes model are satisfied in a sample of left hemisphere stroke patients. First, the present study aims to detect dissociated patterns of performance in the imitation of meaningful and meaningless gestures, both at a group and a single-case level. In agreement with the dual-routes model, we predict that lack of meaningful superiority effect, when the visuo-motor route is spared, would indicate that the visuo-motor route is involved in processing of both meaningful and meaningless gestures and compensate for damage to the semantic route. Instead, significantly poor performance on meaningful gestures, in absence of difficulties in the imitation of meaningless gestures, would suggest that even if the visuo-motor route is intact, it cannot be recruited to imitate meaningful gestures. A second aim is to investigate whether meaningful intransitive gestures and meaningful transitive gestures are supported by distinct cognitive mechanisms and are dissociable in patients with left hemisphere stroke. Following the dual-route model, we predict that it is possible to detect double dissociations on the basis of the type of gesture that is imitated. Finally, the present study aims at exploring whether performance on linguistic or semantic measures is correlated with imitation of transitive or intransitive meaningful gestures, but is dissociable from performance on meaningless gestures imitation. As it was demonstrated in previous studies (Mengotti et al., 2013; Achilles et al., 2016) we predict that meaningful, but not meaningless, gestures would significantly correlate with performance on linguistic tasks that require lexical-semantic access. Furthermore, other studies (Hauk et al., 2004; Tettamanti et al., 2005; Pazzaglia et al., 2008; Sakreida et al., 2013; Desai et al., 2015; see also paragraph 1.2.4) detected a strict association between action word/sentence processing and gesture execution. Thus, we expect to find significant correlations between performance on gesture imitation tasks and verb processing.

2.2 MATERIALS AND METHODS

2.2.1 Participants

Thirty-two patients suffering from left hemisphere stroke lesions (Age: 65.8 ± 13.1; Education: 8.6 ± 4.1; 20 males, 12 females) and 27 healthy participants (Age: 67.8 ± 10.9; Education: 8.9 ± 3.9; 10 males, 17 females) were recruited at “Villa Beretta” Rehabilitation Unit in Costamasnaga (LC, Italy). Patients were included if they were right-handed (as revealed by the Edinburgh Handedness Inventory; Oldfield, 1971), had no previous history of neurodegenerative or psychiatric disease, and showed a relative spared performance in a short-term non-verbal memory task (Corsi test). All participants gave informed consent in agreement with the 1975 Helsinki Declaration as revised in 1983.

2.2.2 Assessment of Apraxia

Participants were tested with two tasks for Ideo-Motor apraxia and one task evaluating pantomime of object use. Since almost all patients suffered from hemiplegia for their right upper limb, all gestures were executed with the left hand/arm. The first task was the Ideo-Motor Apraxia Test (IMAT), developed by De Renzi and colleagues (1980), which comprehends two lists of gestures, one for fingers and one for hand gestures. The test evaluates both meaningless (ML) and meaningful (MF) gestures, presented in intermingled blocks of 3 gestures. For each item, if the participant was able to correctly execute the gesture at first presentation, 3 points were given. If the participant performed the gesture correctly after the second or the third presentation, 2 points and 1 point were assigned, respectively. If the participant failed even after the third presentation, 0 points were assigned. The maximum score for each list was 36 points. The total score was obtained by the sum of the score obtained in the imitation of finger gestures plus the score obtained in the imitation of hand gestures. The maximum total score was, therefore, 72 points, with the cut-off score set at 53 points. Scores between 53 and 62 corresponded to a borderline level. The second gesture imitation task was the Short Test for Ideo-Motor Apraxia (STIMA), developed by Tessari et al. (2011, 2015). This task assessed MF and ML gestures separately. If the participant executed the gesture correctly at first presentation, 2 points were assigned, while 1 point was given for correct execution on second presentation. A fail on second presentation was scored 0 points. The maximum total score for each of the two lists was 36 points. Furthermore, the STIMA allows the calculation of 2 sub-scores for proximal and distal gestures for both lists. This allowed direct comparisons between meaningful proximal gestures (MFP) and meaningless proximal gestures (MLP) and between meaningful distal gestures (MFD) and meaningless distal gestures (MLD). The maximum score for each sub-scales was 18 points. The STIMA also allows application of age and level of education adjustments and calculation of equivalent scores (0 = deficit; 1 = borderline, 3 = normal performance) on the basis of normative data. Since core symptoms of apraxia not only include gesture imitation deficits, but may also comprise difficulties in the execution of object-related gestures, patients were also tested for pantomime of object use (POU; De Renzi et al., 1980). This task required the pantomime of the typical gesture associated with 10 well-known objects (e.g. hammer, fork) on verbal command (i.e. in absence of the real object). If the participant was able to execute the gesture, 2 points were assigned. If the participant failed, the experimenter repeated the verbal command and assigned 1 point if the gesture was executed properly. Otherwise, 0 points were assigned. The cut-off score, reported by De Renzi et al. (1980), was 18 out of 20 maximum points.

2.2.3 Linguistic and Semantic Tasks

All participants completed the Aachen Aphasia Test (AAT; Italian version, Luzzatti et al., 1996), the Naming and Comprehension subtests of the Northwestern Assessment of Verbs and Sentences (NAVS, Italian version, Barbieri et al., 2013), a Semantic Association Task (SAT), and a Visual Completion Task (VCT), that we previously developed for another study (Luzzatti et al., in preparation). The AAT evaluates spontaneous speech, short-term verbal memory and auditory comprehension (Token Test), oral Repetition, Reading and Writing abilities (Dictation by composition and Writing), lexical-semantic production of words and sentences on picture presentation (Naming), and Auditory and Written Comprehension. For each subtest, a level of impairment is available (Minimal, Mild, Medium, and Severe). Likewise the AAT Naming subtest, the NAVS Naming subtest requires to produce the correct verb on picture presentation (e.g. produce the word “watering” when the picture of a man watering plants is presented). In the Comprehension subtest of NAVS, instead, the participant is asked to choose, among four alternatives, which is the correct picture that corresponds to a spoken verb. Likewise other neuropsychological tests for semantic abilities (e.g. the Pyramids and Palm Trees test, Howard & Patterson, 2004), in the SAT the participant is required to associate the object-picture that is located on the top of a card (probe picture) to one of two object-pictures that are located below it. The innovation introduced by this task is the possibility of 4 different scores calculation, corresponding to distinct types of semantic association - *Categorical associations (CA;* the two items belong to the same category, e.g. a giraffe and a zebra); *Encyclopedic associations (EA,* the two items were learnt to be related from school, e.g. cow and cheese); *Functional associations (FA,* the two items can be used together for a common purpose, e.g. screw and screwdriver); *Visual-encyclopedic associations (VEA,* the two items are associated mostly because they were seen together, in spatial proximity, e.g. clown and circus big top). Four practice items (not scored) were presented before the task. Verbal instructions were the following: "Could you please indicate which of the two below pictures is related most, in your opinion, with the picture on the top?". One point was given for each correct answer. The maximum score for each semantic association was 19 points, and 76 points was the total maximum score. An example of cards for each type of semantic association is given in Figure 1. The VCT was developed to test visual semantic competence. It consists in 46 cards, divided into two subtests (animals vs. objects). Each card displays triads of black-and-white drawings, one on top of the card (probe drawing) and two below it (target vs. foil). The probe drawing is an incomplete animal or object, the target drawing is the correct missing part. The foil is always visually plausible. The missing parts can be associated to the incomplete picture by simple transposition, thus not requiring any mental rotation or size manipulation. Participants have to choose the missing part by pointing silently at one of the two drawings on the bottom part of the card. Verbal instructions were the following: "Could you please indicate which of the two below pictures is the correct missing part of the picture on the top?". One practice card (not scored) was given before each subtest. One point was given for each correct response, so that the maximum scoring was 23 for each subtest. An example of card for each subtest is given in Figure 2. In a previous study, we applied the SAT to both healthy participants and patients with fronto-temporal lobar degeneration or Alzheimer's disease. On the basis of healthy participants' performance we calculated cut-off scores for the total task (*cut-off score for total SAT= 50*) and for each subset (*cut-off scores for SAT subsets: CA = 11, EA = 13; FA = 14; VEA = 13*). Results showed that patients with Alzheimer's disease and the semantic variant of fronto-temporal lobar degeneration had idiosyncratic patterns of performance on the four SAT subsets, indicating that this task is suitable to investigate semantic memory deficits and detect different types of semantic association impairment.

Figure 1: Examples of stimuli used in the Semantic Association Task (SAT). On the top, from left to right: Categorical Association (CA), Encyclopedic association (EA). On the bottom, from left to right: Functional association (FA) and Visual-Encyclopedic association (VEA).

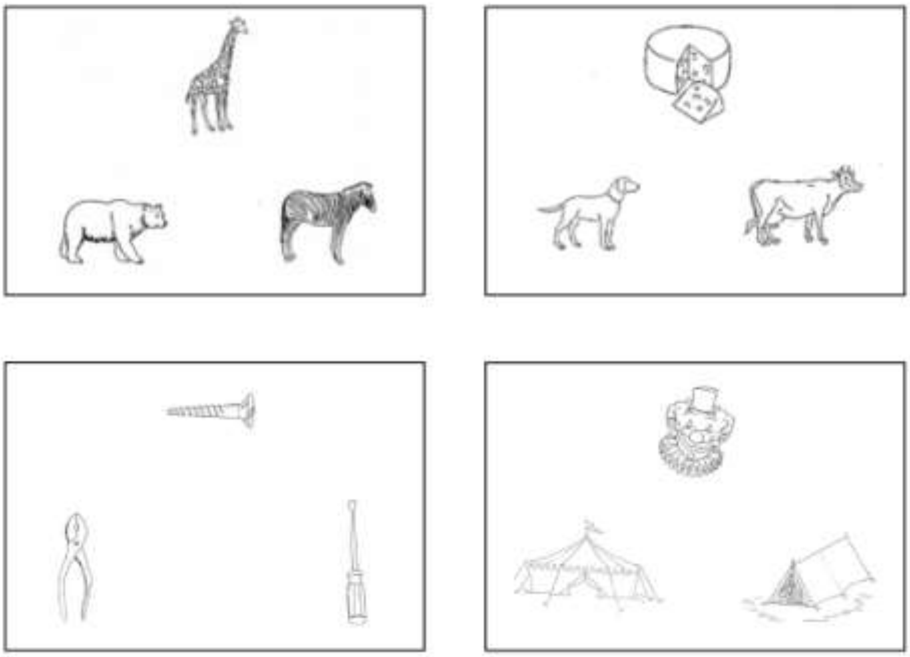
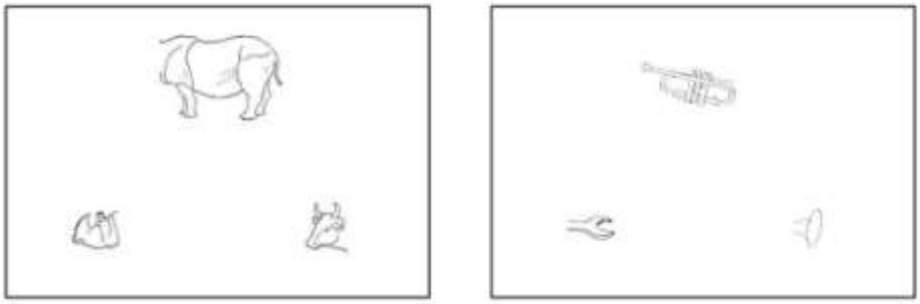


Figure 2: Two examples of stimuli used in the Animals (on the left) and in the Objects (on the right) subtests of the Visual Completion Task (VCT).



2.2.4 Experimental procedure

All patients were initially tested with the AAT, the Corsi Test for non-verbal short memory deficits and the IMAT. Patients who could not perform the IMAT due to difficulties in understanding verbal instructions were not included in the study, as well as patients who were not able to successfully complete a two-cube motor sequence in the Corsi Test. These inclusion criteria were settled in order to prevent gesture imitation difficulties due to severe language comprehension or short-term motor memory deficits. If the patient was included in the study, then he/she completed two subsequent testing sessions of about 30-40 minutes each. Tasks presentation order was randomized across participants. The same procedure was conducted also for healthy participants, who, however, were not tested with the AAT. Healthy participants completed successfully all the tasks in a unique session.

2.2.5 Statistical Analysis

Unless otherwise stated, statistical analysis was conducted with SPSS Statistics, version 25. The first aim of the study was to compare patients' performance on the four types of gesture of the STIMA (MFP, MFD, MLP, MLD) with that obtained by healthy participants, in order to detect possible dissociations. Preliminary analysis of data showed that patients' performance on all apraxia tasks was normally distributed (see Figure 3 and Figure 4), whereas data on healthy participants violated normal distribution assumptions (see Figure 5 and Figure 6) especially because they performed at ceiling in some tasks (e.g. all participants obtained the maximum score in PMF, 11 out of 27 participants obtained the maximum score in POU). Thus, between-groups comparisons were conducted with Mann-Whitney non-parametric test, whereas differences within-groups were explored with Friedman non-parametric test and Wilcoxon-ranks test for post-hoc analysis. However, since none of these tests allowed the interaction of within (type of gesture) and between (groups) factors evaluation, a parametric ANOVA was also conducted. In healthy participants, but not in the patient group, age and educational level significantly correlated with performance on STIMA subtests. Thus, in the within-between factors ANOVA, age and educational level were included as covariates. Since group analyses are based on average means, these methods may not be suitable to detect dissociated patterns. In fact, distinct performances on two tasks might be masked by the group-level trend, or not emerge because of other cases displaying the opposite pattern (Caramazza, 1986; Shallice, 1988). Thus, possible dissociations between performances on MF, relative to ML, gestures were also evaluated at single-case level with Crawford's program

(*Dissocs_Es*, Crawford & Garthwaite, 2005; Crawford et al., 2010). The program allowed calculation of patients' z-scores using healthy participants' means and standard deviations and comparisons across conditions/tasks applying a significance threshold $p < .05$. This test assessed whether the difference between two z-scores found in patients deviated significantly from the difference found in normal subjects. A *Classical* dissociation occurred when the patient was significantly impaired in a task, but did not differ from healthy participants in another task. A *Strong* dissociation, instead, was detected when the patient performed significantly poorer than healthy participants in both tasks, but significantly worse in one of them. Unfortunately, it was not possible to evaluate dissociations between gestures divided by proximal effector due to the fact that healthy participants had a ceiling performance on MFP gestures, which prevented from calculating standard deviations. The second aim of the study was to explore the relationship between distinct praxis measures in patients. Correlation analyses were conducted between each sub-scale of the STIMA and the two De Renzi tests (IMAT and POU). Dissociations between POU and performance on MF gestures, which were both assumed to rely upon a long-term gestural memory, were explored with Crawford's method at a single case level. Finally, the present study aimed at investigating the relationship between praxis and linguistic measures. For this purpose, partial correlations and regression analyses were conducted in the patient group.

Figure 3. Data distribution for STIMA in patients. On the left: MF gestures, on the right: ML gestures. On the top: Total scores, in the middle: Proximal gestures, on the bottom: Distal gestures.

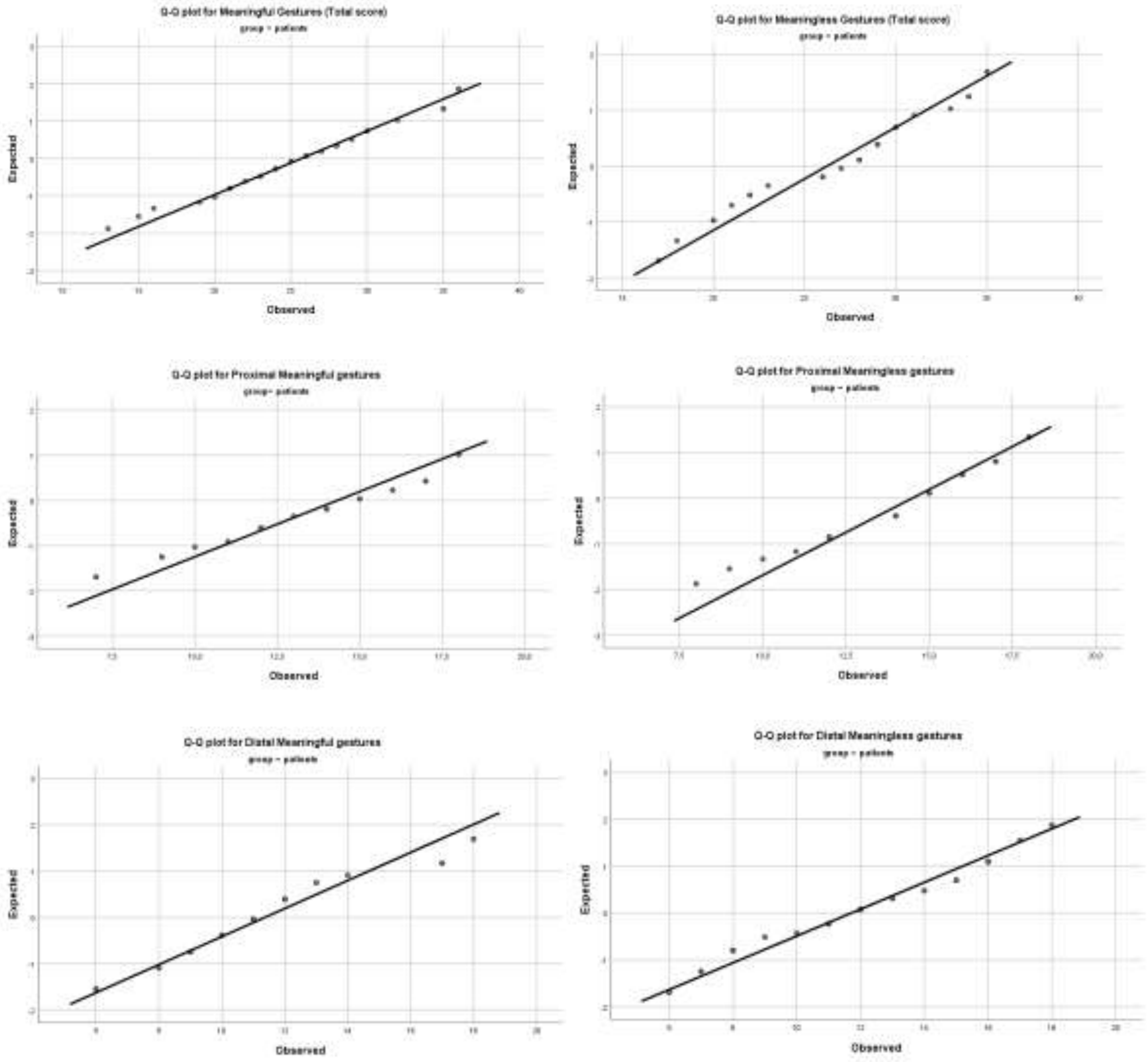


Figure 4. Data distribution for POU (on the left) and IMAT (on the right) in patients.

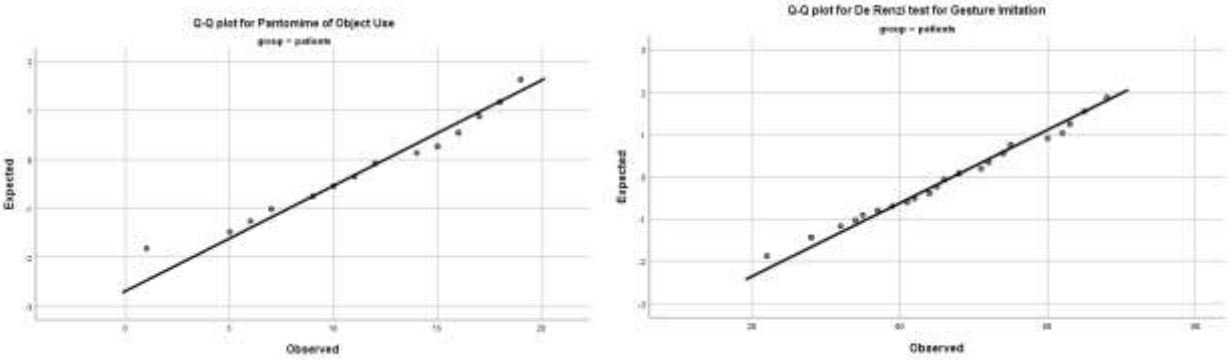


Figure 5. Data distribution for STIMA in healthy participants. On the left: MF gestures, on the right: ML gestures. On the top: Total scores, in the middle: Proximal gestures, on the bottom: Distal gestures.

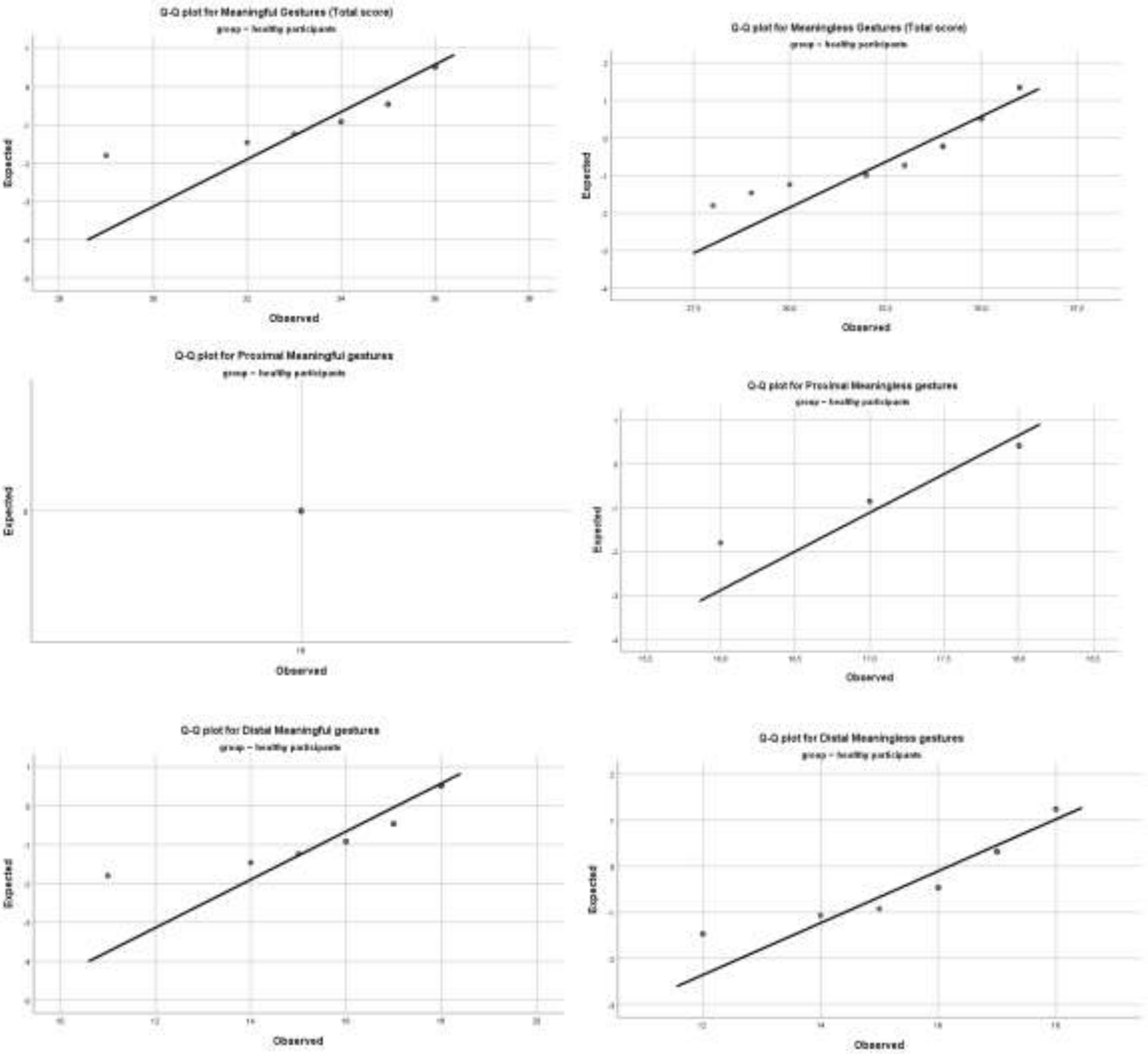
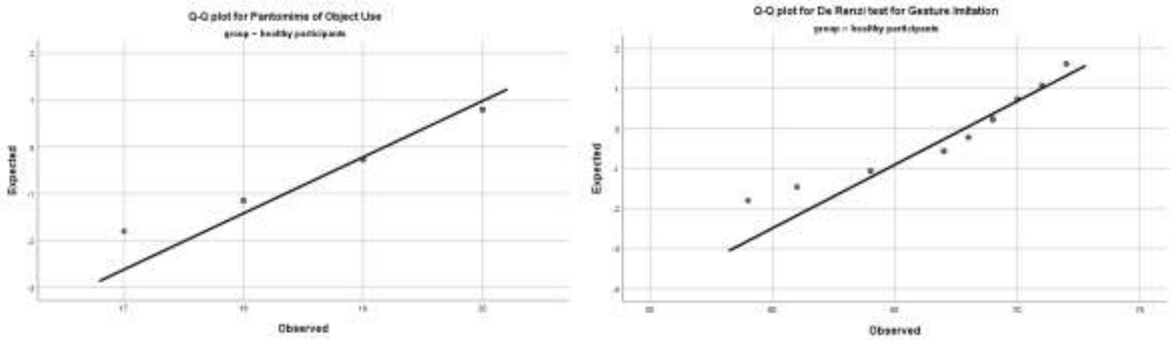


Figure 6. Data distribution for POU (on the left) and IMAT (on the right) in healthy participants.



2.3 RESULTS

2.3.1 Patients description and Neuropsychological evaluation

According to the AAT evaluation, all 32 patients suffered from slight to severe aphasia. On the basis of spontaneous speech evaluation, 14 patients had a fluent form of aphasia, while 18 patients had a non-fluent form of aphasia. Table 1 displays patients' performance on the different AAT subscales and the relative level of impairment. Some patients could not access the preliminary test (i.e. for the Token Test and the Dictation by composition subtests), or had an extremely severe performance on some of the AAT subtests, because of echolalia and automatic elements repetition. Assessment of apraxia revealed that only one patient (case RS) was not impaired on any task, while two patients had an isolated borderline performance on IMAT (case GC and case GP). According to the total score of the IMAT, 22 patients were classified as apraxic, 6 patients performed at a borderline level and 4 patients were not apraxic. Performance on POU was affected in 28 patients and spared in 4 patients. According to the STIMA subscale for MF gestures, 22 patients were classified as apraxic, 3 patients performed at a borderline level, and 7 patients had a spared performance. According to the STIMA subscale for ML gestures, 10 patients were apraxic, 8 patients performed at a borderline level and 14 patients performed within normal ranges. Comparing the equivalent scores (ES) obtained for ML and MF, 10 patients were equally impaired (ES = 0) on both types of gesture, 6 patients were impaired on MF (ES = 0) but spared on ML (ES = 2), 6 patients showed a trend for a relative spared performance on ML (ES = 1) relative to MF (ES = 0) and 6 patients were spared in both gestures (ES = 2). No patients revealed a deficit on ML (ES = 0) but spared performance on MF (ES = 2 or ES = 1). Mean values and ES for the three apraxia tests are reported in Table 2. Performance on the other neuropsychological tests was compared between patients and healthy participants with Mann-Whitney non parametric test. Patients performed significantly worse on the Corsi test, the two NAVS subtests, the total SAT score and all SAT subsets but were comparable to healthy participants on the VCT (Figure 7).

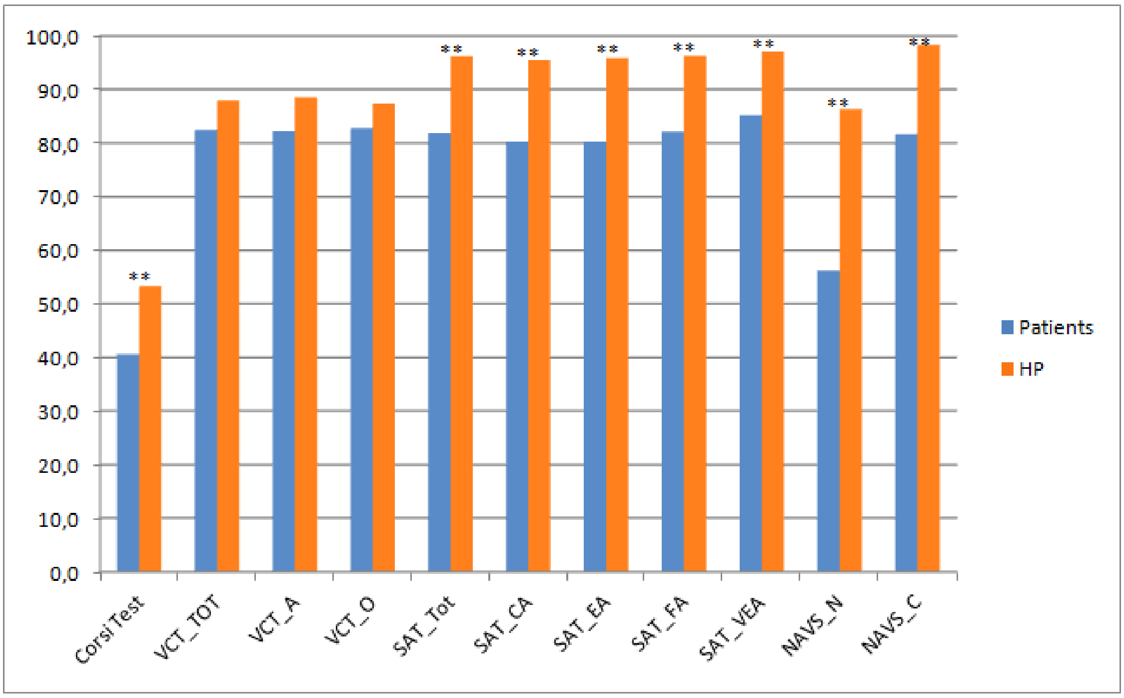
Table 1: Patients' scores on the AAT subtests and relative level of impairment. Legend: F/NF = Fluent/Not Fluent, Token = Token Test, Tok_L = Level of impairment for Token Test, Rep = Repetition, Rep_L = Level of impairment for Repetition, Read = Reading, Read_L = Level of impairment for Reading, Dic = Dictation by composition, Dic_L = Level of impairment for Dictation by composition, Wri = Writing, Wri_L = Level of impairment for Writing, Nam = Naming, Nam_L = Level of impairment for Naming, Comp_O = Oral Comprehension, Comp_O_L = Level of impairment for Oral Comprehension, Comp_W = Written Comprehension, Comp_W_L = Level of impairment for Written Comprehension, n.a. = the patient does not access the preliminary test, -- = null performance because of echolalia or automatic elements repetition.

Case	F/NF	Token	Tok_L	Rep	Rep_L	Read	Read_L	Dic	Dic_L	Wri	Wri_L	Nam	Nam_L	C_O	C_O_L	C_W	C_W_L
AA	F	35	Mild	145	Mild	24	Mild	n.a.	--	--	--	74	Medium	40	Medium	29	Medium
AF	F	19	Minimal	--	--	--	--	n.a.	--	--	--	106	Minimal	56	Minimal	58	Minimal
AG	NF	--	n.a.	--	--	--	--	n.a.	--	--	--	--	--	33	Severe	--	--
AL	NF	--	n.a.	--	--	--	--	n.a.	--	--	--	--	--	44	Medium	29	Medium
AP	NF	50	Medium	--	--	--	--	n.a.	--	--	--	2	Severe	34	Severe	--	--
AS	NF	32	Mild	41	Severe	--	--	n.a.	--	--	--	54	Medium	44	Medium	30	Medium
AV	F	--	n.a.	--	--	--	--	n.a.	--	--	--	--	--	27	Severe	--	--
CC	NF	49	Medium	--	--	--	--	n.a.	--	--	--	--	--	48	Mild	25	Medium
DL	NF	44	Medium	20	Severe	0	Severe	n.a.	--	--	--	3	Severe	46	Medium	41	Medium
EB	NF	31	Mild	135	Mild	26	Mild	5	Medium	--	--	82	Medium	36	Severe	53	Mild
EG	F	--	n.a.	--	--	--	--	n.a.	--	--	--	94	Mild	--	--	--	--
FC	NF	--	n.a.	--	--	--	--	n.a.	--	--	--	--	--	51	Mild	29	Medium
FRC	NF	49	Medium	--	--	--	--	n.a.	--	--	--	--	--	--	--	--	--
FS	NF	44	Medium	68	Medium	0	Severe	0	Severe	0	Severe	0	Severe	43	Medium	7	Severe
GAL	F	30	Mild	52	Severe	10	Medium	n.a.	--	--	--	11	Severe	47	Mild	34	Medium
GC	F	--	n.a.	--	--	--	--	n.a.	--	--	--	97	Mild	43	Medium	43	Medium
GD	F	13	Minimal	136	Mild	28	Mild	n.a.	--	29	Minimal	50	Mild	48	Mild	48	Mild
GL	F	38	Mild	129	Mild	--	--	28	Minimal	29	Minimal	76	Medium	49	Mild	41	Medium
GMF	F	--	n.a.	66	Severe	19	Medium	n.a.	--	--	--	38	Severe	6	Severe	3	Severe
GP	F	5	Minimal	--	--	--	--	n.a.	--	--	--	--	--	--	--	--	--
IS	F	42	Medium	81	Medium	5	Severe	n.a.	--	--	--	54	Medium	46	Medium	41	Medium
LG	NF	46	Medium	38	Severe	0	Severe	n.a.	--	--	--	0	Severe	27	Severe	13	Severe
LM	F	39	Mild	124	Mild	24	Mild	n.a.	--	--	--	78	Medium	26	Severe	31	Medium
LN	NF	38	Mild	124	Mild	24	Mild	8	Medium	9	Medium	68	Medium	46	Medium	30	Medium
LV	NF	--	n.a.	--	--	--	--	n.a.	--	--	--	--	--	8	Severe	--	--
MAC	NF	--	n.a.	--	--	--	--	n.a.	--	--	--	--	--	--	--	--	--
MB	NF	--	n.a.	12	Severe	--	--	n.a.	--	--	--	--	--	36	Severe	10	Severe
MC	NF	50	Medium	6	Severe	3	Severe	n.a.	--	--	--	4	Severe	--	--	--	--
MF	F	--	n.a.	2	Severe	--	--	n.a.	--	--	--	10	Severe	29	Severe	29	Medium
RC	NF	--	n.a.	--	--	25	Mild	n.a.	--	--	--	63	Medium	38	Medium	48	Mild
RS	F	7	Minimal	148	Mild	29	Minimal	30	Minimal	30	Minimal	116	Minimal	58	Minimal	57	Minimal
TC	NF	23	Mild	145	Mild	29	Minimal	21	Mild	--	--	104	Mild	37	Medium	55	Mild

Table 2. Patients' scores on the apraxia Tests. Legend: IMAT = Ideo-Motor Apraxia Test (De Renzi et al., 1980), Fin = gestures executed with Fingers, Han = gestures executed with the Hand , Tot = Total score, Tot_ES = Equivalent score for Total Score, POU = Pantomime of Object Use, STIMA = Short Test for Ideo-Motor Apraxia (Tessari et al., 2011, 2015), MF_r = raw scores for Meaningful gestures, MF_c = corrected scores for Meaningful gestures, MF_ES = Equivalent Scores for Meaningful gestures, ML_r = raw scores for Meaningless gestures, ML_c = corrected scores for Meaningless gestures, ML_ES = Equivalent Scores for Meaningless gestures. In Bold: scores below the cut-off, underlined scores = borderline level. Cut-off scores: IMAT Tot: < 53, POU: < 18, MF < 33.2, ML < 27.8. Borderline level: IMAT Tot: 53 ≤ x ≤ 62, MF: 33.2 ≤ x ≤ 34.0, ML: 27.8 ≤ x ≤ 31.0.

Case	**IMAT**				**POU**	**STIMA**					
	Fin	**Han**	**Tot**	**Tot_ES**		**MF_r**	**MF_c**	**MF_ES**	**ML_r**	**ML_c**	**ML_ES**
AA	30	24	54	1	**15**	27	**31.6**	**0**	29	31.2	2
AF	27	33	60	1	**15**	29	33.9	1	28	32.1	2
AG	16	12	**28**	**0**	**7**	16	**26.7**	**0**	18	**22.3**	**0**
AL	23	21	**44**	**0**	**5**	13	**13.1**	**0**	28	28.0	1
AP	29	26	55	1	**0**	35	35.6	2	34	35.3	2
AS	23	31	54	1	**10**	25	**31.9**	**0**	27	30.6	1
AV	18	23	**41**	**0**	**11**	23	**32.9**	**0**	20	27.9	1
CC	17	17	**34**	**0**	**11**	24	**31.8**	**0**	21	**26.4**	**0**
DL	16	29	**45**	**0**	**16**	30	**32.1**	**0**	29	30.2	1
EB	26	26	**52**	**0**	**12**	21	**29.3**	**0**	31	33.2	2
EG	31	32	63	2	**16**	35	36.0	2	33	36.0	2
FC	23	21	**44**	**0**	**7**	30	34.0	1	28	31.5	2
FRC	19	29	**48**	**0**	**12**	24	**33.0**	**0**	30	34.4	2
FS	31	34	65	2	**14**	21	**25.0**	**0**	26	**27.0**	**0**
GAL	21	25	**46**	**0**	**9**	20	**27.8**	**0**	20	**23.3**	**0**
GC	26	36	62	1	19	36	36.0	2	34	37.4	2
GD	23	29	**52**	**0**	**10**	28	**31.4**	**0**	30	31.5	2
GL	7	21	**28**	**0**	**16**	21	**31.7**	**0**	17	**24.8**	**0**
GMF	26	26	**52**	**0**	**17**	26	**31.1**	**0**	22	**25.2**	**0**
GP	24	31	55	1	19	30	34.1	2	29	32.6	2
IS	20	31	**51**	**0**	**16**	23	**33.1**	**0**	30	34.8	2
LG	18	17	**35**	**0**	**0**	22	**30.2**	**0**	20	**24.5**	**0**
LM	16	21	**37**	**0**	18	25	33.4	1	20	27.9	1
LN	21	21	**42**	**0**	**12**	19	**30.6**	**0**	22	**27.7**	**0**
LV	11	11	**22**	**0**	**1**	15	**23.2**	**0**	17	**19.7**	**0**
MAC	13	19	**32**	**0**	**0**	28	34.3	2	23	30.1	1
MB	30	33	63	2	**6**	32	**33.0**	**0**	35	35.5	2
MC	22	26	**48**	**0**	**9**	26	**33.1**	**0**	26	31.0	1
MF	21	24	**45**	**0**	**0**	28	**32.4**	**0**	26	28.9	1
RC	20	26	**46**	**0**	**12**	30	34.6	2	29	33.6	2
RS	33	35	68	2	18	35	35.8	2	35	36.0	2
TC	18	21	**39**	**0**	**17**	24	**29.4**	**0**	22	**24.7**	**0**

Figure 7. Mean values expressed as percentages for healthy participants and patients in the neuropsychological tasks. Legend: VCT_Tot = Total score for Visual Completion Task, VCT_A = Animal subset of the Visual Completion Task, VCT_O = Object subset of the Visual Completion Task, SAT_TOT = Total score for the Semantic Association Task, SAT_CA = Categorical Associations for the Semantic Association Task, SAT_EA = Encyclopedic Associations for the Semantic Association Task, SAT_FA = Functional Associations for the Semantic Association Task, SAT_VEA = Visual-Encyclopedic Associations for the Semantic Association Task, NAVS_N = Naming subtest of the Northwestern Assessment for Verbs and Sentences , NAVS_C = Comprehension subtest of the Northwestern Assessment for Verbs and Sentences, HP = Healthy Participants.** Significantly different at p<.0001 with Mann-Whitney non-parametric test.



2.3.2 Differences on the four sub-scales of the STIMA

2.3.2.1 Group analysis

Between-groups analysis with Mann-Whitney non-parametric tests revealed that patients scored significantly worse than healthy participants on all types of gesture (Figure 9). Within-groups analyses with Friedman non-parametric tests revealed a significant difference between the 4 types of gesture both in healthy participants (χ^2 *(27, 3) = 40.642, p < .0001*) and in patients (χ^2 *(32, 3) = 35.378, p < .0001*). However, Wilcoxon-ranks tests for paired samples revealed that in healthy participants there was a significant difference both on the basis of meaning (MFD > MLD: *Z = -2.516 , p < .05*; MFP > MLP: *Z -2.887= , p < .01*) and on the basis of the effector (MFP > MFD: *Z = -2.969, p < .01;* MLP > MLD: *Z = -3.781, p < .0001*), while in patients the comparison based on the effector (MFP > MFD: $Z = -3.748, p < .0001;$ MLP > MLD: $Z = -3.994, p < .0001$), but not on meaning (MFD > MLD: $Z = -.583, p > .05$; MFP > MLP: $Z = -.304, p > .05$) was statistically significant. Thus, healthy participants performed significantly better on meaningful than on meaningless gestures and on proximal than on distal gestures. Patients performed significantly better on proximal than on distal gestures, but had comparable performance on meaningful and meaningless gestures. However, distinct patterns of rank-differences were revealed when comparing MF and ML gestures. For example, in the MFP - MLP comparison, 13 patients had the same rank position, 8 patients had a negative rank comparison (MFP < MLP) and 11 patients had a positive rank comparison (MFP > MLP). Similar results emerged also when comparing MFD with MLD. Rank comparisons for healthy participants and patients are reported in Tables 3 and 4. Results of parametric ANOVA with type of gesture (TOF) as within-factor and group (patients versus healthy participants) as between factor, including age and level of education as covariates, revealed similar results of that obtained by the non-parametric analysis (Figure 10). Main effects of type of gesture ($F(1, 165) = 2.842, p < .05$) and group ($F(1, 55) = 64.187, p < .0001$) were statistically significant, with age interacting significantly with type of gesture ($TOF*Age: F(3, 165) = 3.525, p < .05$). Furthermore, the interaction effect between TOF and group was statistically significant ($F(3, 165) = 5.350, p < .01$). Analysis of contrasts confirmed the results obtained with the Wilcoxon-ranks tests, and revealed that distal gestures were performed significantly poorer than proximal gestures (MFP-MFD: $F(1, 55) = 7.753, p < .01$; MLP – MLD: $F(1, 55) = 4.819, p < .05$), irrespective of the meaning (MFP – MLP: $F(1, 55) = .626, p > .05$; MFD – MLD: $F(1, 55) = 2.049, p > .05$).

Figure 9: Between-groups comparisons for each type of gesture. Legend: HP = Healthy Participants, MFP = Meaningful Proximal gestures, MFD = Meaningful Distal gestures, MLP = Meaningless Proximal gestures, MLD = Meaningless Distal gestures. ** = statistically different with p<.0001.

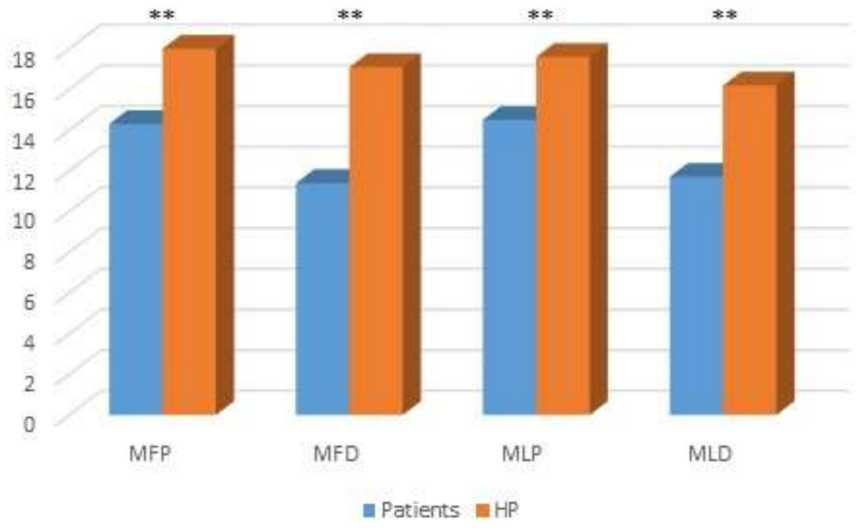


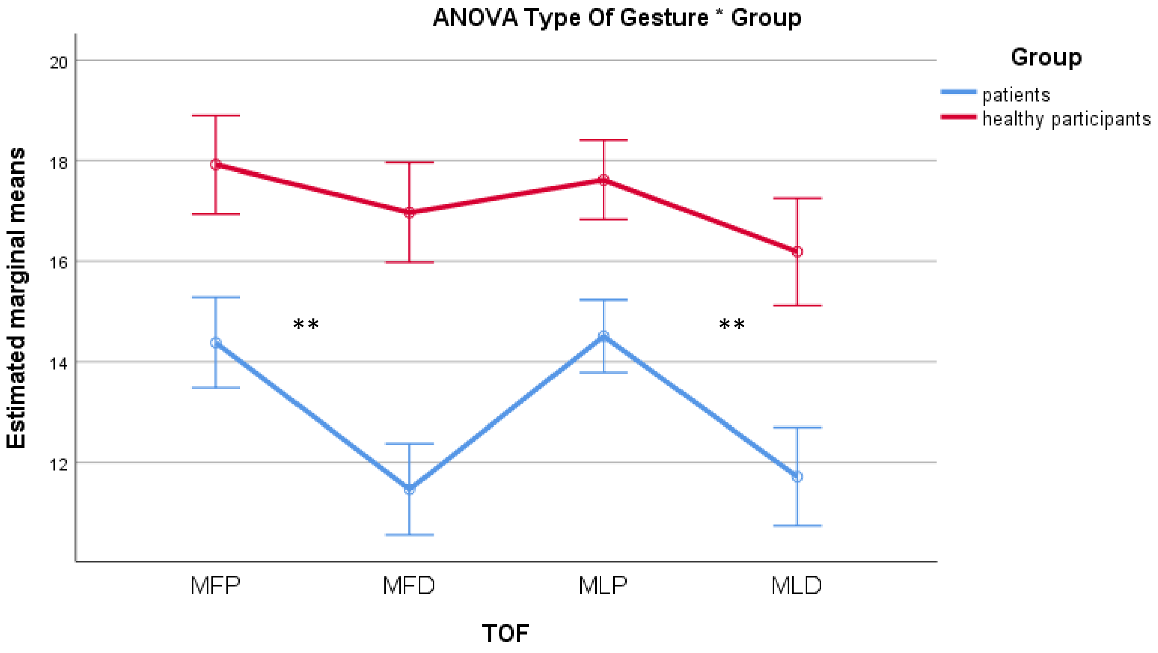
Table 3: Wilcoxon-ranks comparisons on the basis of meaning (MFP – MLP, MFD - MLD) in patients (on the left) and in healthy participants (on the right). Legend: N = number of patients/healthy participants.

Wilcoxon-Ranks Test [a]					**Wilcoxon-Ranks Test [a]**				
		N	**Rank of Mean**	**Sum of Ranks**			**N**	**Rank of Mean**	**Sum of Ranks**
MFP - MLP	*Negative Ranks*	8[b]	12.81	102.50	**MFP - MLP**	*Negative Ranks*	0[b]	0.00	0.00
	Positive Ranks	11[c]	7.95	87.50		*Positive Ranks*	9[c]	5.00	45.00
	Correlations	13[d]				*Correlations*	18[d]		
	Total	32				*Total*	27		
a. group = patients b. MFP < MLP c. MFP > MLP d. MFP = MLP					a. group = healthy participants b. MFP < MLP c. MFP > MLP d. MFP = MLP				
Wilcoxon-Ranks Test [a]					**Wilcoxon-Ranks Test [a]**				
		N	**Rank of Mean**	**Sum of Ranks**			**N**	**Rank of Mean**	**Sum of Ranks**
MFD - MLD	*Negative Ranks*	14[b]	16.32	228.50	**MFD – MLD**	*Negative Ranks*	2[b]	14.25	28.50
	Positive Ranks	14[c]	12.68	177.50		*Positive Ranks*	16[c]	8.91	142.50
	Correlations	4[d]				*Correlations*	9[d]		
	Total	32				*Total*	27		
a. group = patients b. MFD < MLD c. MFD > MLD d. MFD = MLD					a. group = healthy participants b. MFD < MLD c. MFD > MLD d. MFD = MLD				

Table 4: Wilcoxon-ranks comparisons on the basis of the effector (MFP - MFD, MLP - MLD) in patients (on the left) and in healthy participants (on the right).

Wilcoxon-Ranks Test [a]					**Wilcoxon-Ranks Test [a]**				
		N	**Rank of Mean**	**Sum of Ranks**			**N**	**Rank of Mean**	**Sum of Ranks**
MFP – MFD	*Negative Ranks*	4[b]	12.75	51.00	**MFP – MFD**	*Negative Ranks*	0[b]	0.00	0.00
	Positive Ranks	26[c]	15.92	414.00		*Positive Ranks*	11[c]	6.00	66.00
	Correlations	2[d]				*Correlations*	16[d]		
	Total	32				*Total*	27		
a. group = patients b. MFP < MFD c. MFP > MFD d. MFP = MFD					a. group = healthy participants b. MFP < MFD c. MFP > MFD d. MFP = MFD				
Wilcoxon-Ranks Test [a]					**Wilcoxon-Ranks Test [a]**				
		N	**Rank of Mean**	**Sum of Ranks**			**N**	**Rank of Mean**	**Sum of Ranks**
MLP - MLD	*Negative Ranks*	6[b]	7.50	45.00	**MLP – MLD**	*Negative Ranks*	1[b]	5.50	5.50
	Positive Ranks	25[c]	18.04	451.00		*Positive Ranks*	19[c]	10.76	204.50
	Correlations	1[d]				*Correlations*	7[d]		
	Total	32				*Total*	27		
a. group = patients b. MLP < MLD c. MLP > MLD d. MLP = MLD					a. group = healthy participants b. MLP < MLD c. MLP > MLD d. MLP = MLD				

Figure 10. Comparisons between patients and healthy participants on the 4 types of gesture (TOF). ** =Significant interaction between groups and the two types of gesture (MFP vs. MFD and MLP vs. MLD).



Covariates included in the model are evaluated at the following values: Age = 66.73, Educational level = 8.78

Error Bars: 95% Confidence Interval

2.3.2.2 Single-case analysis

Group analysis revealed that patients were significantly more impaired than healthy participants on all types of gesture, but particularly on distal gestures. In fact, no statistical difference between performance on MF and ML was revealed, indicating a lack of meaningful superiority effect, which was evident, instead, in healthy participants. However, Wilcoxon-rank analyses highlighted a comparable number of patients having negative and positive ranks when contrasting meaningful with meaningless gestures. Thus, possible dissociations on meaningful and meaningless gestures were also explored at single-case level with Crawford's method. Raw scores and relative z-scores for ML and MF gestures and presence/absence of dissociation for each patient are displayed in Table 5. One patient (EB) was completely spared in ML gestures but significantly impaired in MF gestures, satisfying criteria for a *Classical* dissociation. Seven patients were significantly more impaired, than healthy participants, on both types of gesture, but had a significantly lower performance on MF than on ML gestures, satisfying criteria for a *Strong* dissociation. Other two patients (IS, FRC) satisfied criteria for a *Strong* dissociation as well, but the pattern was really close to that of a *Classical* dissociation, with more severe impairment for MF gestures (z-scores = -7.5 and -6.8 respectively) than for ML gestures (z-scores = -1.9, $p = .041$). A comparable impairment on both types of gesture was detected in 17 patients, who did not exhibit a dissociated pattern. In one case (MB) performance was slightly affected for MF gestures only (z = -1.9, $p = .041$). The remaining four patients, instead, had a spared performance on both types of gesture. When comparing the two distal subscales (MFD and MLD), results were partially in agreement with those on total scores. All significant dissociations revealed worse performance on MF than on ML gestures. In line with total scores results, cases EB and FRC satisfied criteria for a *Classical* dissociation and four cases (AL, IS, LV, FS) satisfied criteria for a *Strong* dissociation. However, four patients who had satisfied criteria for a *Strong* dissociation when considering total scores (LN, AS, AA, AG) had comparable performance on MF and ML distal gestures. Furthermore, three cases (FC, MC, GD) who had comparable performance on MF and ML gestures when considering total scores, showed dissociated patterns when comparing distal gestures. Results of single-case analysis on the discussed relevant cases are reported in Table 6.

Table 5. Single-case analyses to detect dissociations between MF and ML gestures. Legend: Z-MF = Z-score for Meaningful gestures, p_MF = level of significance for an impairment on meaningful gestures, Z-ML = Z-score for Meaningless gestures, p_ML = level of significance for an impairment on meaningless gestures, Dissoc = type of dissociation, p_Dissoc = level of significance for dissociations, No Diss = absence of dissociation, Pattern = Pattern of dissociation, MF < ML= significantly greater impairment on MF than on ML gestures, MF=ML = no statistical difference between MF and ML, Norm = Performance within normal ranges. In bold: significantly impaired relative to healthy participants (p < .05).

Patient	**MF**	**ML**	**Z-MF**	***p_MF***	**Z-ML**	***p_ML***	**Dissoc**	***p_Diss***	**Pattern**
EB	21	31	**-8.7**	*p < .0001*	**-1.4**	*p > .05*	Classical	*p < .0001*	MF < ML
AA	27	29	**-4.9**	*p < .0001*	**-2.3**	*p < .05*	Strong	*p < .01*	MF < ML
AG	16	18	**-11.8**	*p < .0001*	**-7.7**	*p < .0001*	Strong	*p < .01*	MF < ML
AL	13	28	**-13.6**	*p < .0001*	**-2.8**	*p < .0001*	Strong	*p < .05*	MF < ML
AS	25	27	**-6.2**	*p < .0001*	**-3.3**	*p < .01*	Strong	*p < .05*	MF < ML
FRC	24	30	**-6.8**	*p < .0001*	**-1.9**	*p < .05*	Strong	*p < .05*	MF < ML
FS	21	26	**-8.7**	*p < .0001*	**-3.8**	*p < .001*	Strong	*p < .001*	MF < ML
IS	23	30	**-7.5**	*p < .0001*	**-1.9**	*p < .05*	Strong	*p < .001*	MF < ML
LN	19	22	**-9.9**	*p < .0001*	**-5.7**	*p < .0001*	Strong	*p < .01*	MF < ML
LV	15	17	**-12.4**	*p < .0001*	**-8.2**	*p < .0001*	Strong	*p < .01*	MF < ML
AF	29	28	**-3.7**	*p < .001*	**-2.8**	*p < .01*	No Diss	*p > .05*	MF = ML
AV	23	20	**-7.5**	*p < .0001*	**-6.7**	*p < .0001*	No Diss	*p > .05*	MF = ML
CC	24	21	**-6.8**	*p < .0001*	**-6.2**	*p < .0001*	No Diss	*p > .05*	MF = ML
DL	30	29	**-3.1**	*p < .01*	**-2.3**	*p < .05*	No Diss	*p > .05*	MF = ML
FC	30	28	**-3.1**	*p < .01*	**-2.8**	*p < .01*	No Diss	*p > .05*	MF = ML
GAL	20	20	**-9.3**	*p < .0001*	**-6.7**	*p < .0001*	No Diss	*p > .05*	MF = ML
GD	28	30	**-4.4**	*p < .001*	**-1.9**	*p < .05*	No Diss	*p > .05*	MF = ML
GL	21	17	**-8.7**	*p < .0001*	**-8.1**	*p < .0001*	No Diss	*p > .05*	MF = ML
GMF	26	22	**-5.6**	*p < .0001*	**-5.7**	*p < .0001*	No Diss	*p > .05*	MF = ML
GP	30	29	**-3.1**	*p < .01*	**-2.3**	*p < .05*	No Diss	*p > .05*	MF = ML
LG	22	20	**-8.1**	*p < .0001*	**-6.7**	*p < .0001*	No Diss	*p > .05*	MF = ML
LM	25	20	**-6.2**	*p < .0001*	**-6.7**	*p < .0001*	No Diss	*p > .05*	MF = ML
MAC	28	23	**-4.4**	*p < .0001*	**-5.3**	*p < .0001*	No Diss	*p > .05*	MF = ML
MB	32	35	**-1.9**	*p < .05*	0.6	*p > .05*	No Diss	*p > .05*	MF = ML
MC	26	26	**-5.6**	*p < .0001*	**-3.8**	*p < .001*	No Diss	*p > .05*	MF = ML
MF	28	26	**-4.4**	*p < .001*	**-3.8**	*p < .001*	No Diss	*p > .05*	MF = ML
RC	30	29	**-3.1**	*p < .01*	**-2.3**	*p < .05*	No Diss	*p > .05*	MF = ML
TC	24	22	**-6.8**	*p < .0001*	**-5.7**	*p < .0001*	No Diss	*p > .05*	MF = ML
AP	35	34	-0.04	*p > .05*	0.1	*p > .05*	No Diss	*p > .05*	Norm
EG	35	33	-0.04	*p > .05*	-0.4	*p > .05*	No Diss	*p > .05*	Norm
GC	36	34	0.57	*p > .05*	0.1	*p > .05*	No Diss	*p > .05*	Norm
RS	35	35	-0.04	*p > .05*	0.6	*p > .05*	No Diss	*p > .05*	Norm

Table 6. Patients who satisfied criteria for a dissociations between MFD and MLD gestures and patients who did not reach criteria but had shown a dissociation when comparing total MF and ML gestures. Legend: Z-MFD = Z-score for Meaningful Distal gestures, p_MFD = level of significance for an impairment on meaningful distal gestures, Z-MLD = Z-score for Meaningless Distal gestures, p_MLD = level of significance for an impairment on meaningless distal gestures, Dissoc = type of dissociation, p_Dissoc = level of significance for dissociations, No Diss = absence of dissociation, Pattern = Pattern of dissociation, MFD < MLD = significantly greater impairment on MFD than on MLD gestures, MFD=MLD = no statistical difference between MFD and MLD. In bold: significantly impaired relative to healthy participants (p < .05).

Patient	**MFD**	**MLD**	**Z_MFD**	***p_MFD***	**Z_MLD**	***p_MLD***	**Dissoc**	***p_Diss***	**Pattern**
EB	10	16	**-4.4**	< .0001	-0.1	> .05	Classical	< .01	MFD < MLD
FC	12	16	**-3.1**	< .01	-0.1	> .05	Classical	< .05	MFD < MLD
FRC	9	15	**-5.1**	< .0001	-0.7	> .05	Classical	< .05	MFD < MLD
GD	10	14	**-4.4**	< .0001	-1.2	> .05	Classical	< .05	MFD < MLD
AL	6	11	**-6.9**	< .0001	**-2.9**	< .01	Strong	< .01	MFD < MLD
IS	8	13	**-5.7**	< .0001	**-1.8**	< .05	Strong	< .01	MFD < MLD
FS	6	11	**-6.9**	< .0001	**-2.9**	< .01	Strong	< .01	MFD < MLD
LV	6	9	**-6.9**	< .0001	**-4.0**	< .001	Strong	< .01	MFD < MLD
MC	8	12	**-5.7**	< .0001	**-2.3**	< .05	Strong	< .01	MFD < MLD
AA	13	15	**-2.6**	< .01	-0.7	> .05	No Diss	> .05	MFD = MLD
AG	9	8	**-5.1**	< .0001	**-4.6**	< .0001	No Diss	> .05	MFD = MLD
AS	10	12	**-4.4**	< .0001	**-2.3**	< .05	No Diss	> .05	MFD = MLD
LN	9	8	**-5.1**	< .0001	**-4.6**	< .0001	No Diss	> .05	MFD = MLD

2.3.3 Relationship between Apraxia measures

The IMAT total score significantly correlated with all STIMA scores, but *Pearson's r-values* were particularly higher when considering the Total STIMA score (*r = .785, p < .0001*), and the STIMA subscales for meaningless gestures (ML total score: *r = .823, p < .0001*; MLP: *r = .748, p < .0001*; MLD: *r = .713, p < .0001*) than correlations between IMAT and STIMA subscales for Meaningful gestures (MF Total score: *r = .624, p < .0001*; MFP: *r = .563, p < .01*, MFD: *r = .520, p < .01*). Correlation between POU and IMAT total score was less significant (*r = .407, p = .031*), whereas POU and STIMA were significantly correlated when considering all sub-scales involving meaningful gestures (MF Total score: *r = .533, p < .01*; MFP: *r = .484, p < .01*; MFD: *r = .492, p*

$< .01$) and the proximal sub-scale of meaningless gestures (MLP: $r = .492$, $p < .01$). The strong relationship between IMAT and STIMA total scores was confirmed also by with a chi-squared test comparing praxis outcomes (norm, borderline, deficit) predicted by the two distinct tasks ($\chi^2(4) = 12.583$, $p < .05$). Dissociated patterns of performance between POU and STIMA subscale for MF gestures were explored with Crawford's method. Since performance on POU was completely null in four cases (MF, LG, AP, MAC), we excluded them from this analysis, which was conducted on the remaining 28 patients. Results are displayed in Table 7. Two cases (RS, GC) did not differ from healthy participants in both POU and STIMA. Six patients were equally impaired in both tasks, thus not satisfying criteria for a dissociation. The analysis detected double *Classical* and *Strong* dissociations, with 13 patients who performed significantly worse on POU than on MF gestures (1 *Classical* and 12 *Strong* dissociations), and 7 patients who performed significantly worse on MF gestures than on POU (2 *Classical* and 5 *Strong* dissociations).

Table 7. Single-case analysis for dissociated patterns in POU and MF gestures. Legend: Z-MF = Z-score for Meaningful gestures, p_MF = level of significance for an impairment on meaningful gestures, Z-ML = Z-score for Meaningless gestures, p_ML = level of significance for an impairment on meaningless gestures, Dissoc = type of dissociation, p_Dissoc = level of significance for dissociations, No Diss = absence of dissociation, Pattern = pattern of dissociation, MF < POU = significantly greater impairment on MF gestures than on POU, POU < MF= significantly greater impairment on POU than on MF gestures POU=MF = equally affected performance on MF and on POU, Norm = performance within normal ranges. In bold: significantly impaired relative to healthy participants (p < .05).

Patient	MF	POU	Z-MF	***p_MF***	Z-POU	***p_POU***	Dissoc	***p_Diss***	Pattern
GP	30	19	**-3.1**	*p < .01*	-0.2	*p > .05*	Classical	*p < .01*	MF < POU
LM	25	18	**-6.2**	*p < .0001*	-1.4	*p > .05*	Classical	*p < .0001*	MF < POU
FS	21	14	**-8.7**	*p < .0001*	**-6.3**	*p < .0001*	Strong	*p < .05*	MF < POU
GL	21	16	**-8.7**	*p < .0001*	**-3.8**	*p < .001*	Strong	*p < .0001*	MF < POU
GMF	26	17	**-5.6**	*p < .0001*	**-2.6**	*p < .01*	Strong	*p < .01*	MF < POU
IS	23	16	**-7.5**	*p < .0001*	**-3.8**	*p < .001*	Strong	*p < .01*	MF < POU
TC	24	17	**-6.8**	*p < .0001*	**-2.6**	*p < .01*	Strong	*p < .001*	MF < POU
EG	35	16	-0.04	*p > .05*	**-3.8**	*p < .001*	Classical	*p < .001*	POU < MF
AG	16	7	**-11.8**	*p < .0001*	**-14.7**	*p < .0001*	Strong	*p < .01*	POU < MF
AL	13	5	**-13.6**	*p < .0001*	**-17.1**	*p < .0001*	Strong	*p < .01*	POU < MF
AS	25	10	**-6.2**	*p < .0001*	**-11.1**	*p < .0001*	Strong	*p < .05*	POU < MF
AV	23	11	**-7.5**	*p < .0001*	**-9.8**	*p < .0001*	Strong	*p < .05*	POU < MF
CC	24	11	**-6.8**	*p < .0001*	**-9.8**	*p < .0001*	Strong	*p < .01*	POU < MF
FC	30	7	**-3.1**	*p < .01*	**-14.7**	*p < .0001*	Strong	*p < .0001*	POU < MF
GAL	20	9	**-9.3**	*p < .0001*	**-12.3**	*p < .0001*	Strong	*p < .01*	POU < MF
GD	28	10	**-4.4**	*p < .001*	**-11.1**	*p < .0001*	Strong	*p < .0001*	POU < MF
LV	15	1	**-12.4**	*p < .0001*	**-21.9**	*p < .0001*	Strong	*p < .05*	POU < MF
MC	26	9	**-5.6**	*p < .0001*	**-12.3**	*p < .0001*	Strong	*p < .0001*	POU < MF
MB	32	6	**-1.9**	*p < .05*	**-15.9**	*p < .0001*	Strong	*p < .0001*	POU < MF
RC	30	12	**-3.1**	*p < .01*	**-8.7**	*p < .0001*	Strong	*p < .0001*	POU < MF
AA	27	15	**-4.9**	*p < .0001*	**-5.1**	*p < .0001*	No Diss	*p > .05*	POU = MF
AF	29	15	**-3.7**	*p < .001*	**-5.1**	*p < .0001*	No Diss	*p > .05*	POU = MF
DL	30	16	**-3.1**	*p < .01*	**-3.8**	*p < .001*	No Diss	*p > .05*	POU = MF
EB	21	12	**-8.7**	*p < .0001*	**-8.7**	*p < .0001*	No Diss	*p > .05*	POU = MF
FRC	24	12	**-6.8**	*p < .0001*	**-8.7**	*p < .0001*	No Diss	*p > .05*	POU = MF
LN	19	12	**-9.9**	*p < .0001*	**-8.7**	*p < .0001*	No Diss	*p > .05*	POU = MF
GC	36	19	0.57	*p > .05*	-0.2	*p > .05*	No Diss	*p > .05*	Norm
RS	35	18	-0.04	*p > .05*	-1.4	*p > .05*	No Diss	*p > .05*	Norm

2.3.4. Relationship between Praxis and Linguistic tasks

Due to the high number of included variables and multiple comparisons, only correlations with Pearson's coefficient $r \geq .40$ and p *value* $< .01$ were considered as having great relevance. Total STIMA scores and STIMA subscales for distal gestures did not significantly correlate with any of the linguistic measures, as well as POU performance. Significant correlations were detected between meaningful proximal gestures of STIMA and the functional subset (FA) of the SAT ($r = .480, p = .006$). Regression analysis revealed that performance on FA subset significantly predicted performance on the imitation of MFP gestures (B *coefficient* $= .565$, β *coefficient* $= .480$, $F(1, 29) = 8.703$, $p < .01$, $R^2 = .231$). As far as meaningless gestures are concerned, performance on the proximal subscale of STIMA significantly correlated with the Comprehension subtest of NAVS ($r = .557, p = .001$), the functional subset of SAT ($r = .548, p = .001$) and the SAT Total score ($r = .507, p = .004$). Results obtained by the multiple regression analysis with backward method revealed that the SAT total score was excluded from the final significant model. In addition, performance on verbs comprehension (NAVS_C) and on the FA subset of SAT (SAT_FA) did not significantly predict the performance on imitation of meaningless gestures (NAVS_C: $F(2, 28) = 8.515, p = .071$; SAT_FA: $F(2, 28) = 8.515, p = .09$). As regards IMAT, significant correlations were found with SAT_FA ($r = .480, p < .01$), NAVS_C ($r = .460, p < .01$) and Corsi Test ($r = .457, p < .01$). Regression analysis with backward method excluded the SAT_FA and performance on Corsi Test from the analysis and revealed that performance on verbs comprehension (NAVS_C) had a significant effect (B *coefficient* $= 1.270$, β *coefficient* $= .460$, $F(1, 29) = 8.703$, $p < .01$, $R^2 = .185$, $\Delta R^2 = -.073$).

2.4 DISCUSSION

In the field of apraxia, according to the dual-routes model (Rothi et al., 1991; Cubelli et al., 2000), different types of gesture (meaningful and meaningless) are processed by two distinct cognitive and neural pathways (semantic route and visuo-motor route) and may be selectively impaired in patients with brain lesions. Meaningful intransitive gestures (i.e. symbolic gestures, such as waving goodbye) may be stored in a gestural long-term memory and easily accessed or retrieved when we interact with other people. Similarly, the specific gesture required to execute transitive meaningful actions (i.e. actual object use and pantomime of object use) may be stored in a particular gestural memory as well. However, the way in which different cognitive processes underlying these three types of action interact is still a matter of debate (see paragraphs 1.1.4 and 2.1). In the present study, the ability to imitate meaningful (MF) and meaningless (ML) gestures, as well as to pantomime the use of an object (POU) on verbal command, was investigated in patients with left hemisphere stroke and compared to data obtained in a sample of healthy participants. Previous studies demonstrated that the semantic route and the visuo-motor route were differentially engaged to process MF and ML gestures, respectively, but this was true only when the two types of gesture were presented in separated lists (Tessari & Rumiati, 2004; Tessari et al., 2007). For this reason, dissociations between MF and ML gestures were explored using the Short Test for Ideo-Motor Apraxia (STIMA, Tessari et al., 2011, 2015). This test allowed the separate evaluation of MF and ML gestures and the differentiation, within each list, between gestures executed with the hand/fingers (proximal (P) gestures), and gestures executed with the arm (distal (D) gestures). Between groups analysis see paragraph 2.3.2.1 and Figure 9) showed that patients performed significantly worse than healthy participants in each type of gesture, irrespective of meaning (MF vs. ML) and effector (P vs. D). Results obtained by the within group analysis (Tables 3 and 4) revealed a significantly worse performance on distal relative to proximal gestures, irrespective of meaning (MFD < MFP, MLD < MLP), in both patients and healthy participants. Conversely, when considering meaning differences, healthy participants performed significantly better on MF than on ML gestures (MFD > MLD, MFP > MLP), whereas patients showed no difference on the two types of gesture (MFD = MLD, MFP = MLP). These results were also confirmed by the between-within ANOVA (Figure 10), which revealed significant principal effects of both between (group) and within (type of gesture) factors and a significant interaction effect when contrasting gestures with different effectors (MFP vs.

MFD, MLP vs. MLD) but not when contrasting gestures with and without meaning (MFP vs. MLP, MFD vs. MLD). The lack of a meaningful superiority effect in left hemisphere stroke patients was already reported by previous studies (Buxbaum et al., 2007; Mengotti et al., 2013) and is in agreement with dual-routes model predictions when there is damage of the semantic route. In fact, when the semantic route was disrupted, the inability to access the semantic meaning of the gesture in memory would provoke a selective deficit in the imitation of MF gestures. One interesting question emerged from literature (Bartolo et al., 2001; Tessari et al., 2007) is whether an intact visuo-motor route may compensate for a semantic route deficit, enabling to process MF gestures as they are new, unknown gestures. The lack of difference between MF and ML performance may support the hypothesis that a relatively spared visuo-motor route was engaged to imitate both types of gesture. However, since group analyses are based on average means, single-case dissociated patterns could be masked by the group trend. Thus, single-case analysis for imitation if MF vs. ML gestures were conducted with Crawford’s method (paragraph 2.3.2.2). One patient (EB) showed a C*lassical* dissociation, with spared performance on ML gestures and severely affected performance on MF gestures. Comparable *Classical* dissociations were detected also in other 3 patients (FC, FRC, GD) when comparing results on distal MF and ML gestures. This pattern of impairment rules out the possibility that these patients used the intact visuo-motor route to imitate also MF gestures and compensate for the semantic route damage. As it was previously suggested (Tessari et al., 2007), even though damaged, the semantic route could have been triggered anyway because of spared recognition abilities of gestures meaning. In this case, it is supposed that the action input lexicon would be spared, while the impairment would occur at the level of the action semantic system. Thus, in patients who showed a *Classical* dissociation, the semantic route might be triggered anyway, preventing a switch to the intact non-semantic direct route. Significant *Strong* dissociations for a worse performance on MF than on ML gestures were detected in 9 patients, when considering MF and ML total scores, and in one further case (MC) when considering distal sub-scales. This pattern indicates that both semantic and visuo-motor routes were damaged, but patients had more difficulties in imitating meaningful gestures. Although the dual-route model predicts that the two routes may be selectively impaired, single-case analysis did not reveal any dissociated case for MF > ML. Unfortunately, due to ceiling performance obtained by healthy participants, it was not possible to evaluate single-case dissociations for proximal gestures, which could lead to further dissociated patterns. The second aim of the study was to explore the relationship between distinct praxis measures (see paragraph 2.3.3). Patients' total scores (MF + ML gestures) on IMAT and STIMA significantly correlated with each other and predicted the presence/absence of apraxia in a parallel way. Performance on POU significantly correlated with all STIMA sub-scales involving the imitation of MF gestures, suggesting a relationship between gesture execution tasks that require an access to gesture meaning. However, double dissociated patterns between POU and execution of MF gestures at single-case level were detected (one *Classical* and 12 *Strong* dissociations favoring MF on POU, two *Classical* and five *Strong* dissociations favoring POU on MF). These results are in line with dual-routes model, which hypothesize different action input lexicons for transitive (POU) and intransitive meaningful gestures (Cubelli et al., 2000). In agreement with this view, pantomime of object use and imitation of communicative gestures were found to be supported by distinct neural pathways (Dressing et al., 2016). Furthermore, a recent study showed that pantomime of object use and imitation of gestures (both meaningful and meaningless) rely upon two distinct components of gestures representations (Buxbaum et al., 2014). Specifically, object-action posture representations were particularly necessary for object-use pantomime, while visuo-motor information about hand/arm postures, relative to other body parts, was crucial for gestures imitation. However, dissociations between POU and MF gestures may be due not only to distinct input lexicon representations but to the different input modality used in the two tasks. In fact, POU was evaluated on verbal command, thus requiring a first auditory comprehension step and a lexical-semantic access to the corresponding object, whereas MF gestures imitation required only a visual analysis of the presented gesture. The current study is not able to fully discriminate between these two hypotheses. However, performance on POU did not significantly correlate with the Oral Comprehension subtest of the AAT (*r = .206, p = .33*), even when considering only patients who performed below the cut-off (*r = .103, p = .68*). Furthermore, POU errors were predominantly body-part as objects (e.g. use the index finger as a rubber) and clumsiness (e.g. make a left-to-right movement, rather than a rotatory movement, while showing how to use a key) rather than unrecognizable gestures. Thus, dissociations between POU and MF are more likely explained by distinct cognitive pathways required to process these two types of gestures. The third aim of the study was to explore the relationship between praxis and linguistic measures (paragraph 2.3.4). According to the dual-routes model, the semantic route, through which meaningful gestures are produced by access to their meaning in the action semantic system, could also support some aspects of linguistic tasks. This means that imitation of MF gestures, but not ML gestures, may be correlated/associated with measures of aphasia or other linguistic measures. Recent studies showed that, in left hemisphere stroke patients, the performance on MF, but not on ML, gestures was significantly influenced by the severity of aphasia as measured by the Token Test (Achilles et al., 2016), and significantly correlated with performance on the Naming and Repetition subtests of the AAT (Mengotti et al., 2013). In our sample, no significant correlation was detected between the MF subscale of STIMA and these measures (Token test: *r* = -*.348*, Naming*: r = .246*, Repetition: *r = -.140*, all *p values > .05*). However, a significant correlation emerged between the MFP subscale of STIMA and performance on the functional association (FA) subset of TAS. Moreover, linear regression analyses highlighted that performance on MFP was significantly predicted by performance on FA. None of STIMA subscales for the imitation of ML, instead, was significantly predicted by any of the linguistic or semantic measures, although significant correlations were detected between MLP and verbs comprehension, total SAT score, and FA subset of SAT. These results are in agreement with dual-routes model predictions for significant associations between praxis and linguistic/semantic tasks when considering MF gestures, but not when considering ML gestures. The lack of association between AAT aphasia subtests is not in contrast with previous studies (Mengotti et al., 2013; Achilles et al., 2016) but rather suggests that MF gestures and lexical/linguistic or semantic tasks dynamically interact with each other. As suggested by Mengotti et al. (2013), cognitive mechanisms underlying lexical-semantic processes for language and gestures are dissociable, but may interact with each other, and brain networks can partially overlap, depending on the task. The FA subset of the SAT investigates the ability to associate objects that played complementary roles when performing an action (i.e. toothpaste and toothbrush). This type of association have also been called “thematic relations involving action” (Kalénine et al., 2009) and was found to be significantly associated with gesture recognition tasks and with regions of the left posterior temporal cortex supposed to be involved in processing information about objects manipulation (Kalénine et al., 2016). Thus, our results suggest that, in our patient sample, cognitive and neural mechanisms supporting the imitation of meaningful gestures significantly interacted with those mechanisms underlying processing of action semantics information. Moreover, these results suggest that, in our sample of patients, the impairment of the semantic route occurred at the level of the action semantic system or, at least, after the input action lexicon. This evidence supports the hypothesis that in patients with selective deficits for MF gestures the intact visuo-motor route could not be activated to imitate MF gestures because the semantic route was triggered at the first stage (input lexicon). Interestingly, performance on POU did not correlate with any of the linguistic or semantic measures, although the verbal input of the test. Furthermore, although the FA subset of SAT investigated the ability to associate objects that are used together in a purposeful action, requiring access to object-action representations, performance on this task did not correlate with POU. This result was unexpected, since many studies showed that pantomime of object use relies upon retrieval of semantic knowledge about the shape and functional and manipulation properties of objects (Randerath et al., 2011; Baumard et al., 2016). However, the kind of semantic representation involved in the FA subset of SAT relies upon functional aspects of objects rather than their manipulation. Dissociations in an object matching task favoring function over manipulation knowledge of objects were reported in apraxic relative to non-apraxic patients (Buxbaum & Saffran, 2002) and recent studies suggested that object affordance plays a crucial role in object-related actions (Buxbaum, 2017). Thus, the type of semantic knowledge required to successfully execute POU may be different from the semantic information involved to associate objects in the FA subset of SAT. To sum up, the present study supports the existence of multiple routes that differently process meaningless gestures, meaningful intransitive gestures and meaningful transitive gestures. Even if the three praxis tasks were highly correlated, significantly greater impairment for meaningful gestures, than for meaningless, and double dissociated patterns between transitive and intransitive meaningful gestures were detected. In addition, data showed that poor performance on MF intransitive gestures, but not on ML gestures, was significantly predicted by performance on a semantic association task requiring to associate objects that are used together in a purposeful action. This result supports recent studies (Mengotti et al., 2013; Goldenberg & Randerath, 2015) highlighting that, although cognitive and neural mechanisms underlying the production of meaningful gestures and lexical-semantic tasks are dissociable, they interact in a dynamic way and may partially overlap depending on the task and on which aspects are examined. One limitation of the present study was that single-case analysis for dissociations could not be conducted for proximal gestures due to ceiling performance of healthy participants on MFP. In addition, the relationship between different types of knowledge about objects (e.g. functional and manipulation properties of objects) and the execution of object-related actions (e.g. pantomime) remains unclear. Unexpectedly, no significant correlation was found between performance on the verb processing task (NAVS), although a large amount of studies demonstrated that verb processing activates areas that are also active during action observation and imitation (see paragraph 1.2.4). This evidence led us to focus on the relationship between semantic knowledge and praxis, and especially those aspects of semantic knowledge that can be related to action.

CHAPTER 3. STUDY 2: THE BRAIN KNOW-HOW. A BEHAVIORAL AND METABOLIC IMAGING STUDY OF DISSOCIATIONS BETWEEN OBJECT SEMANTICS AND ACTION SEMANTICS

3.1 INTRODUCTION

The first experiment of the present work highlighted a significant relationship between meaningful gestures imitation and the performance in a semantic task in which participants were required to associate objects that could be used together in a same action. The second experiment focused on the representation of different types of action concepts in the brain. Conceptual representations of objects comprise object attributes whose knowledge is acquired through sensory, motor and affective experiences with the object (Allport, 1985; Shallice, 1988; Barsalou, et al., 2003; Mahon et al., 2007; Martin, 2007, 2016; Patterson et al., 2007; see Mahon & Hickok, 2016 for a review). For instance, the concept of 'scissors' encloses knowledge about shape (a pair of overlapping metal blades whose edges slide past each other, attached to two rings), color (usually steel color), manipulation (make a shearing action with ring-shaped thumb and index finger) and purpose of use (e.g. cutting a piece of paper). Models of semantic memory (Warrington & Shallice, 1984; Allport, 1985; Damasio, 1990; Martin, 2007, 2016) state that the degree to which the sensory and motor systems were engaged during our experience with the object defines the relative degree to which the object concept is based on sensory rather than functional attributes. While visual perceptual features (e.g. color and shape) are assumed to be crucial for living object concepts (animals, fruits, vegetables), allowing us to categorize and distinguish them (e.g. a donkey and a zebra are classified as animals because they have four legs and a tail, but may be discriminated thanks to their different coats), functional properties are assumed to be crucial for non-living concepts, including tools (e.g. a pair of scissors and a knife are objects used 'for cutting', whereas a garden shovel and a spade are objects used 'for digging' [Shallice, 1988; Warrington & Shallice, 1984]). Instances of attributes that define a tool concept are the specific gestures that need to be performed for its appropriate use, i.e. manipulation knowledge (Buxbaum & Kalénine, 2010), the goal that can be achieved with it, i.e. functional knowledge (Buxbaum & Saffran, 2002), and its context of use (Martin & Chao, 2001). All these attributes are acquired during actual tool use, controlled by sensory and motor areas (Beauchamp & Martin, 2007). Whether manipulation and functional knowledge are embodied in the same neural structure responsible for actions execution is still debated in the literature. Several studies have shown that motor and sensory regions like the ventral premotor area, the inferior frontal gyrus and the inferior parietal lobule are activated not only when we perform an action, but also during tasks of action understanding and recognition (Gallese et al., 1996; Grèzes et al., 1998; Buccino et al., 2004b), object recognition (Gallese & Lakoff, 2005), or even reading of action words: in an event-related functional Magnetic Resonance Imaging (fMRI) study, Hauk et al. (2004) found that the activity in the premotor and primary motor cortex was modulated in a somatotopic manner when healthy participants passively read verbs indicating actions performed with different body parts (e.g. "pick", "lick", "kick"). These observations have been interpreted as evidence of an automatically-induced retrieval of representation of observed actions or of actions associated with an observed object (Rizzolatti & Craighero, 2004). In this theoretical framework, labeled as "embodied theory of cognition", manipulation knowledge is grounded in the same brain areas responsible for action execution (Barsalou et al., 2003). A particularly strong inference of the embodiment theory is that if the sensorimotor system is damaged the patient is not only unable to use the object correctly, but also unable to recognize it (Gallese & Lakoff, 2005). However, some studies have provided results in contrast with this prediction. Negri and colleagues (2007a) showed that left hemisphere-damaged patients who were impaired in pantomime execution and/or action imitation were not necessarily impaired also in object and pantomime recognition. On the same line, a study of five cases with congenital bilateral upper limb dysplasia found no deficits in eight different tasks of recognition and interpretation of actions (e.g. recognition of pantomimes, actions naming, judgment of accuracy of performance of gestures), even if these patients had never executed any upper limbs action, and should thus have never developed any representation of such actions, according to the embodiment perspective (Vannuscorps & Caramazza, 2016). An alternative view of organization of conceptual knowledge about object manipulation and function (van Elk et al., 2014; Martin, 2016) proposes that the output of a network of motor and sensory areas, termed action semantics, is integrated to become part of a multi-modal object representation (Buxbaum & Saffran, 2002). Action semantics includes "knowing-how" to use the object (manipulation knowledge), "knowing-that" the object is used for a specific purpose (functional knowledge) and knowing the proprioceptive and sensory experience associated with object use (van Elk et al., 2014). Manipulation knowledge in the "knowing-how" system is mapped to the dorsal stream for object processing, while functional knowledge in the "knowing-that" system is associated with the ventral stream for object processing (Binkofski & Buxbaum, 2013). Finally, the "hub and spokes" model of semantic memory (Patterson et al., 2007; Lambon Ralph et al., 2010) suggests that conceptualization stems from the joint action of both modality-specific information derived from association cortices and a cross-modal interaction zone (the hub) located in the anterior temporal lobes (ATLs). Likewise distributed models, in this approach different kinds of object information arise from distinct modality-specific cortices (i.e. sensorial and motor cortices, and association areas along the dorsal and ventral streams), but, unlike distributed models, this theory proposes that information about objects from each of these modality-specific areas (the spokes) converge in the ATLs (the hubs). The hub combines such information, including function and manipulation knowledge, and builds a supra-modal representation of the object. According to this model, manipulation and function knowledge are represented in two distinct spokes, but, since both types of information converge in the ATLs, damage to the hub would cause impairment of both categories of object knowledge. In agreement with this theoretical framework, a repetitive transcranial magnetic stimulation (rTMS) study on healthy participants demonstrated that, while the left inferior parietal lobule (IPL) belonging to the dorsal stream had a specific role in matching tools according to the way in which they are manipulated, the left anterior temporal lobe was crucial for matching tools according to both manipulation and function (Ishibashi et al., 2011). These findings suggest that, although knowledge for tool manipulation may be stored in the left IPL, both function and manipulation knowledge converge in the ‘hub’. Consistent with models claiming distinct neural loci for function and manipulation knowledge, several studies on clinical and healthy populations have shown that these two types of knowledge are dissociable at both a behavioral and neuroanatomical level. Within a sample of left-stroke patients, some (those with apraxia) were exclusively or predominantly impaired in selecting, among three alternatives, the two objects that shared the same manipulation (e.g. a key and a screwdriver), whereas others were more or only impaired in selecting the two objects that had the same function (e.g. a stapler and cellophane tape) (Buxbaum & Saffran, 2002). An uneven impairment of functional and manipulation knowledge has also been found in various studies carried out on subjects with temporal damage. These patients performed more poorly when asked to verbally describe the correct purpose of an object or its context of use relative to the correct manipulation (Sirigu et al., 1991), to identify the two objects that share the same function relative to the same manipulation (Negri et al., 2007b), or to match a target tool with its corresponding recipient-object for a specific purpose (e.g. a hammer and a nail) relative to the pantomime of its use (e.g. hammering) (Jarry et al., 2016). Two fMRI studies in healthy participants investigated brain activations related to performance on a judgment task with pairs of objects that could share the same function or be manipulated in the same way. The study highlighted overlapping patterns of activation in a large left-hemisphere network including the prefrontal and premotor cortex, the posterior middle temporal gyrus (pMTG) and IPL, but significant greater activations were found for manipulation than for functional knowledge in the left IPL and adjacent inferior parietal sulcus (Boronat et al., 2005; Kellenbach et al., 2003). In an fMRI study, Canessa et al. (2008) contrasted manipulation and context of use with an objects matching task, and further confirmed that the caudal intraparietal sulcus and rostral IPL, and also the dorsal premotor cortex, were more strongly activated by the former type of knowledge, whereas specific activations in the retrosplenial and anterior temporal cortex were associated with context of use. Further, virtual lesions induced with rTMS in the left supramarginal gyrus (SMG) have been found to interfere with a judgment task in which subjects had to decide whether two objects were used by adopting the same hand posture, while performance on an action recognition task and two conceptual judgement tasks investigating functional knowledge and context of use was unaltered (Pelgrims et al., 2011). Finally, an fMRI study on young healthy participants using multivoxel pattern analysis found significant activation in a left fronto-parietal network, including the primary motor cortex and the anterior intraparietal sulcus, for manipulation, while purpose of use activated the left medial temporal cortex (Chen et al., 2015). To sum up, a considerable number of studies carried out from different theoretical perspectives, and performed in the fields of apraxia as well as in semantic memory disorders, tried to address the issue of separation between manipulation and functional knowledge, and their relationship with object concepts. The aim of the present study was to further investigate this topic by assessing whether different types of action semantics can be selectively impaired in patients with different forms of degenerative dementia: SD, CBS and Posterior Cortical Atrophy (PCA). These disorders offer the possibility to associate distinct neuropsychological profiles with different atrophy patterns. SD patients suffer a breakdown of concepts due to degeneration within the ATLs (Gorno-Tempini et al., 2011), while PCA patients exhibit a progressive decline in visuoperceptual and praxic skills due to parieto-occipito-temporal atrophy (Crutch et al., 2012), and CBS patients often suffer from limb apraxia in association with other motor and cognitive disturbances, and prevalent fronto-parietal degeneration (Armstrong et al., 2013). All participants to the study performed a category decision task in which they had to judge whether pairs of objects share the same context of use (e.g. scalpel - syringe), purpose (pen - keyboard) or way of manipulation (drill - hairdryer). Since function and context of use conditions were associated to different neural areas in previous neuroimaging studies (Kellenbach et al., 2003; Boronat et al., 2005; Canessa et al., 2008), they were investigated separately. We first assessed possible dissociations among conditions in each individual patient with a single case analysis. Based on prior evidence (Patterson et al., 2007), according to the Hub and Spokes theory, SD patients would be equally poor at all three conditions, due to their generalized semantic deficits, and their degree of impairment would be proportional to impairment on neuropsychological measures of semantic abilities. Presence of dissociated pattern in this patient population would be hardly interpreted within the Hub and Spokes framework, and other models for semantic memory should be taken into account (e.g. Martin, 2016). With respect to CBS patients, they may present with Ideo-Motor apraxia and other motor features, but, typically, no semantic deficit. They might therefore be impaired in the manipulation condition, in the presence of a relatively spared performance in function and context of use associations. Results on PCA patients, conversely, are less predictable. These patients may be impaired on all types of judgment, in a similar way to SD patients, due to dysfunction at the level of both occipito-temporal and parietal regions. However, unlike SD patients, their performance on the experimental task might be proportional to Ideo-Motor apraxia and visuo-constructive or visuo-spatial deficits, rather than to semantic measures. Secondly, in subgroup of patients who had undergone brain 18F-Fluoro-deoxy-glucose Positron Emission Tomography (FDG-PET), performance on each of the three conditions was correlated with distribution of hypometabolism. Significant correlations between poor performance on Manipulation and/or Purpose conditions and hypometabolism in premotor and/or motor areas would support the strong version of the embodiment theories (Gallese & Lackoff, 2005). Conversely, significant associations between affected performance on Manipulation and areas of the ventro-dorsal stream would account for the embodiment multi-modal theories (van Elk et al., 2014; Martin, 2016) but also for the Hub and Spokes theory (Ishibash et al., 2011). Moreover, significant hypometabolism in the ATLs in relation to poor performance on all semantic associations would be in agreement with the Hub and Spokes theory. Dissociated and widespread activations in the ventro-dorsal and the ventral stream, in relation to the three semantic conditions, would be in agreement with multi-modal claim in the field of embodiment (Mahon et al., 2007; Martin, 2016).

3.2 MATERIALS AND METHODS

3.2.1 Participants

Neurodegenerative patients were recruited from the memory clinic of S. Gerardo Hospital, Monza, Italy. They were 26, 12 (46.2%) female, with a mean age of 70.2 years ±6.7 and mean education of 8.4 years ±4.3, and had a diagnosis of SD (n= 9), Corticobasal Syndrome (CBS) (n= 9) or Posterior Cortical Atrophy (PCA) (n= 8) according to standardized or consensus criteria (Armstrong et al., 2013; Crutch et al., 2012; Gorno-Tempini et al., 2011). Patients were included if they had predominant lexical-semantic impairment or visuo-spatial and visuo-motor deficits (such as impaired copy of complex figure and Ideo-Motor apraxia) or a combination of these two deficits. They all underwent a general neuropsychological battery including the Mini-Mental State Examination (MMSE, Measso et al., 1993), Attentional Matrices (AM, Spinnler & Tognoni, 1987), Digit span (Monaco et al., 2013), Rey Auditory Verbal Learning Test (RAVLT, Carlesimo et al., 1996), copy of Rey-Osterrieth Complex Figure (ROCF, Carlesimo et al., 2002), Category and Letter fluency (Novelli et al., 1986), the Frontal Assessment Battery (FAB, Appollonio et al., 2005), Benton Judgement of Line Orientation (BJLO, Benton et al., 1993), De Renzi's Test of Ideo-Motor Apraxia (De Renzi et al., 1980), Pyramids and Palm Trees test (PPT, Howard & Patterson, 1992) and a non-standardized Picture naming test composed by 28 pictures from the Snodgrass and Vanderwart (1980) series (12 living and 16 non-living items). Twenty healthy participants were also enrolled as control group: 11 female (55.0%), with mean age of 73.5 years ± 6.1, mean education of 7.5 years ± 2.8 and mean MMSE score of 29.0 ± 1.2. All participants to the study gave their informed consent before being included, and the study was conducted in conformity with the Declaration of Helsinki and approved by our institution ethics committee. Seventeen out of 26 patients also underwent brain FDG-PET suitable for semiquantitative analysis with Statistical Parametric Mapping (SPM) 8 (Wellcome Department of Imaging Neuroscience, London, UK) and were included in the metabolic imaging study. Table 1 shows their average scores as a group on the general neuropsychological battery.

Table 1. Neuropsychological scores of the 17 neurodegenerative patients who were included in the metabolic study. All scores are age-, sex- and/or education-adjusted, unless otherwise stated.

	n. cases	Max	Cut off	Mean	SD	Min-Max
Mini Mental State Examination	17	30	≥ 24.3	24.1	3.1	17.5-29
Attentional Matrices	16	60	≥ 31.0	36.4	13.4	12-54
Digit span	17	9	≥ 5.3	5.2	1.6	2-9.7
Rey Auditory Verbal Learning Test:						
-*Immediate recall*	15	65	≥ 28.0	32.1	10.4	17.1-50.5
-*Delayed recall*	15	15	≥ 4.8	6.3	3.4	0-12
Copy of Rey-Osterrieth Complex Figure	17	36	≥ 28.9	19.9	12.9	0-37.8
Category fluency	17	-	≥ 25.0	22.8	10.4	3-41
Letter fluency	17	-	≥ 17.0	23.8	8.3	8-38
Frontal Assessment Battery	16	18	≥ 13.5	12.1	3.5	7.3-17.5
Benton Judgement of Line Orientation	12	30	≥ 19	15.5	7.6	0-28
De Renzi's Test of Ideo-Motor Apraxia*:						
-*Right limb*	14	72	≥ 53	50.3	16.7	24-71
-*Left limb*	14	72	≥ 53	48.4	17.4	17-72
Picture Naming*	15	28	≥ 24**	14.5	8.1	0-26
Pyramid and Palm Trees	15	52	≥ 40.2	40.9	5.9	27.1-48.7

*raw score; **two standard deviations from the mean score of the healthy participants group

3.2.2 Assessment of object and action semantics with the Category Decision task

Knowledge of the most typical context in which objects are used, of the purpose of their utilization, and of the correct way to manipulate them was evaluated with a Category Decision task in which subjects had to decide whether two objects presented in a verbal written form on a computer screen were used in the same environment (e.g. scalpel - syringe; Context condition), had a similar function (pen - computer keyboard; Purpose condition), or were handled with the same postures or gestures (drill - hairdryer; Manipulation condition). In each ‘yes’ pair the objects shared only the characteristic assessed in that specific condition. Stimuli used in the three conditions were matched for frequency, familiarity, age of acquisition and imaginability. Frequency was extracted from a database available online (*COLFIS*, Bertinetto et al., 2005), while the other psycholinguistic variables were scored by 25 raters on a 7-point Likert scale. Each condition was assessed with two blocks of 20 ‘yes’ trials and two blocks of 20 ‘no’ trials preceded by some practice trials and presented in randomized order (2 blocks x 40 pairs = 80 pairs). For each condition, ten out of 80 pairs (five related and five unrelated) were excluded from the analysis having been failed by at least 30% of healthy participants. The task maximum score was therefore 70 for each condition.

3.2.3 Statistical analysis

Single-case analysis was carried out with the software *Dissocs_ES.exe* (Crawford et al., 2010; Crawford & Garthwaite, 2005), which calculates patients' z-scores using healthy participants’ means and standard deviations and compares them across conditions/tasks applying a significance threshold $p < 0.05$, assessing whether the difference between two scores found in patients deviates significantly from the difference found in normal subjects. Following this analysis, patients were grouped according to the presence and pattern of significant dissociations between conditions. Subgroups were then compared for socio-demographic and neuropsychological features using Kruskall-Wallis test followed by Mann-Whitney in SPSS 25.0 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp.). More conservative non-parametric statistics was preferred given the small subgroups size. Significance was set at $p < 0.01$ in order to control for Type 1 error but avoiding loss of statistical power implied in Bonferroni’s correction.

3.2.4 Metabolic neuroimaging protocol in the group of 17 patients

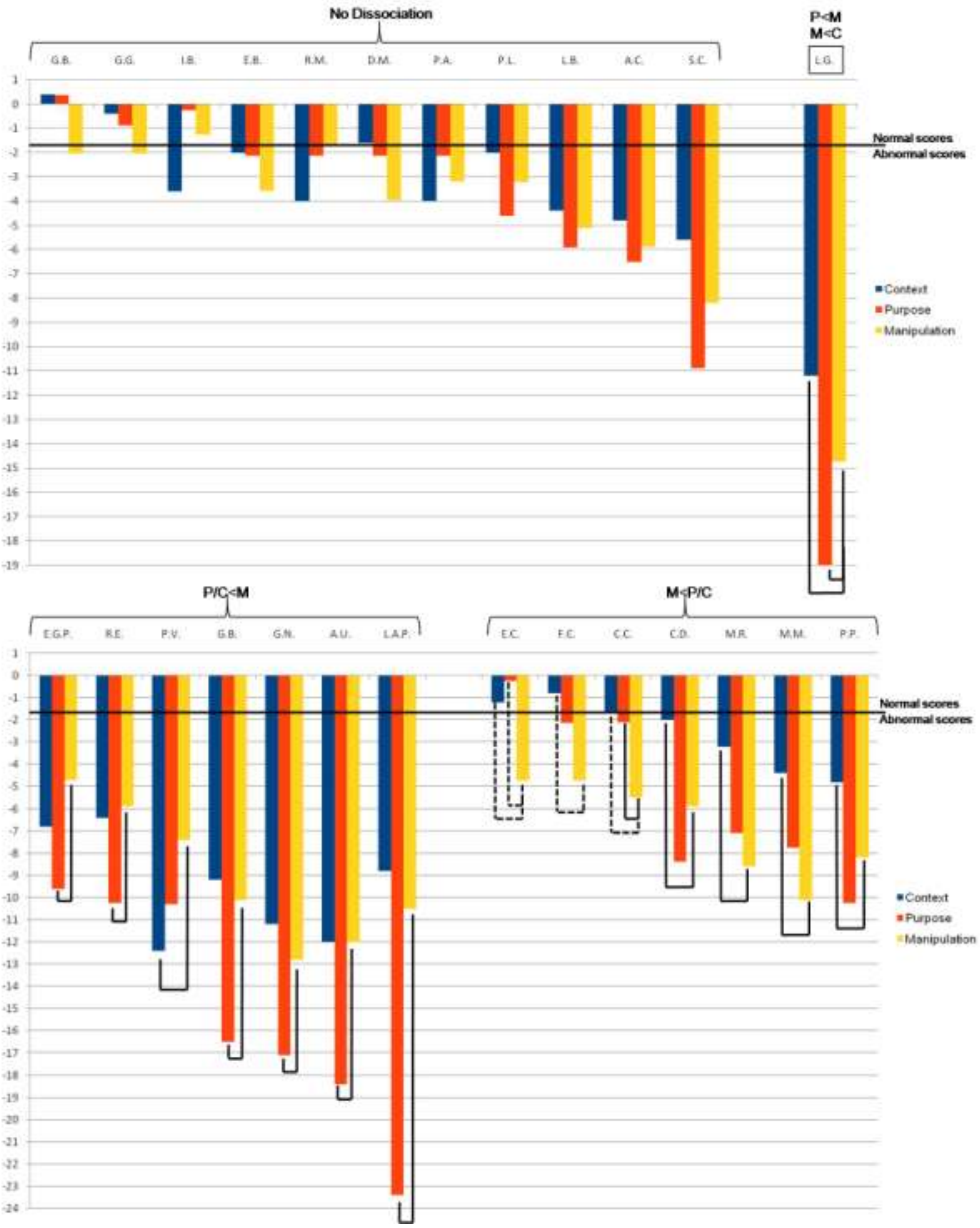
FDG-PET was performed with General Electric Discovery LS PET/CT in the Department of Nuclear Medicine of S. Gerardo Hospital, Monza. Before the metabolic exam, patients fasted for at least six hours. After being measured blood glucose levels, they received an intravenous bolus of approximately 200 MBq of 18F-FDG. They then lied supine in a quiet, dimly-lit room, for approximately 45 mins, and were finally transferred to the scanner. First a CT scan was performed for attenuation correction, then PET images were acquired for 15 mins, with a thickness of 3.27 mm and a matrix of 128x128 pixels. Subsequent image reconstruction followed an ordered subset expectation maximization (OSEM) algorithm. Using SPM8, images were reoriented along the anterior-posterior commissure, spatially normalized to the Montreal Neurological Institute reference space using a FDG-PET dementia-specific template, and smoothed with an isotropic 3D Gaussian kernel of 16 mm FWHM. Correlation between scores obtained on the three conditions of the Category Decision task and FDG-uptake was assessed through linear regression analysis, with age, sex and MMSE score as covariates of no interest. Distribution of hypometabolism in subgroups of patients with/without dissociations between conditions was compared using two-sample t-test, with age and sex as covariates, with scans from a group of 30 controls acquired on the same PET scanner (disease-free oncologic patients undergoing PET for disease staging, 14 women, with a mean age of 66.5 years, a mean education of 9.1 years and a mean MMSE score of 28.9, who signed an informed consent before being included in the study). For all analyses significance threshold was set at $p < 0.001$ uncorrected and clusters were taken into account if they had a minimum size of 100 voxels. Anatomical labelling of loci of decreased FDG uptake was carried out with Talairach's atlas and Automatic Labelling atlas using the SPM8-integrated toolbox WFU_PickAtlas. All PET images of patients included are displayed in Appendix A.

3.3 RESULTS

3.3.1 Performance on the three semantic conditions of the Category Decision Task

Crawford's analyses for dissociations revealed that 20 out of 26 patients (76.9%) had an impairment in the Context of Use, 22 (84.6%) in the Purpose, and 24 (92.3%) in the Manipulation condition. Figure 1 depicts all single cases' zeta-scores for the three types of semantic association. Zeta-scores allowed us to distinguish between three patient subgroups. A first subgroup (eleven patients, 42.3%) did not satisfy Crawford's criteria for a dissociation between Manipulation and the other two conditions (G.B., G.G., I.B., E.B., R.M., D.M., P.A., P.L., L.B., A.C., S.C.) (*NoDiss* subgroup). A second subgroup enclosed seven patients (26.9%) who were more impaired in Manipulation than in the Context of use condition (five cases) or more impaired in Manipulation than both Context and Purpose conditions (case E.C. and case C.C.) (M<P/C subgroup). Seven patients (26.9%), instead, were relatively spared in Manipulation but more impaired in Purpose condition (E.G.P., E.R., G.B., G.N., A.U., L.A.P.) or in both Context and Purpose conditions (case P.V.) (P/C<M subgroup). One patient, L.G., showed both P<M and M<C dissociations. In the P<M subgroup, purpose was more damaged than Context (P<C), satisfying criteria for a *Strong* dissociation, in five cases (R.E., G.B., G.N., A.U., L.A.P.). This latter dissociation was also found in four cases of the *M<P/C* subgroup (C.D., M.R., M.M., P.P.), in one patient with no other dissociation (S.C.) and in case L.G. The opposite dissociation (C<P) emerged in only one patient, I.B. (*Classical* dissociation).

Figure 1. Zeta scores obtained by each of the 26 neurodegenerative patients included in the case series on the three conditions (Context, Purpose and Manipulation) of the Category Decision task. Significant dissociations between Manipulation and the other two conditions are indicated by dotted (Classical dissociation) or solid (Strong dissociation) lines.



3.3.2 Differences between the three patient subgroups

Table 2 shows the socio-demographic, clinical and neuropsychological features of each patient in the *NoDiss*, *M<P/C* and *P/C<M* subgroups and L.G. Results of comparison between subgroups are reported in Table 3. There was no statistically significant difference for age, education or sex distribution. Average scores on Context and Purpose conditions were worse for *P/C<M* patients than for both the other subgroups, who had a proportionate performance. Manipulation was performed similarly by *P/C<M* and *M<P/C* patients, and both groups performed worse in Manipulation than *NoDiss* patients. Prevalence of the various clinical phenotypes was similar between *NoDiss* and *M<P/C* patients, while the *P/C<M* subgroup had a lower proportion of CBS and a higher proportion of SD cases in comparison to the *M<P/C* subgroup. Patients in *P/C<M* subgroup had a better performance on Digit span and copy of ROCF, but a worse performance on Picture naming, than *M<P/C* patients. They also had a worse performance on Picture naming and Category fluency, but a better performance on copy of ROCF and on BJLO, in comparison to *NoDiss* patients. The patient showing the P<M and M<C dissociations, L.G., was a 70 year old man with 10 years of schooling and a MMSE score of 16. His final diagnosis was CBS based on biomarkers, neuroimaging and clinical evolution, but he presented with an atypical onset characterized by early lexical-semantic deficits. At time of inclusion in the study he showed severe deficits on Picture naming (3) and Letter fluency (4.0), moderate Ideo-Motor apraxia (right limb: 40, left limb: 44) and impairment on Digit span (3.75), copy of ROCF (23), Category fluency (14.0) and PPT (29.0), and relative sparing of the other cognitive domains. At neurological examination he also showed elements of Gerstmann syndrome (dysgraphia, acalculia, digital agnosia, and left/right disorientation). His FDG-PET scan evidenced hypometabolism in the left temporo-parietal and inferior frontal cortex and precuneus, right superior temporal gyrus and bilateral cingulum, and basal ganglia.

Table 2. Characteristics of the 26 patients included in the case series grouped according to presence and pattern of dissociation across conditions on the Category Decision task. Scores are sex-, age- and/or education-adjusted, unless otherwise stated. Abnormal scores are in bold. * = raw scores. LEGEND: Edu= education, MMSE= MiniMental State Examination, AM= Attentional Matrices, RAVLT Imm/Del= Rey-Auditory Verbal Learning Test Immediate/Delayed recall; ROCF= Rey-Osterrieth Complex Figure; FAB= Frontal Assessment Battery; BJLO= Benton Judgment of Line Orientation; IMA= Ideo-Motor Apraxia; PPT= Pyramids and Palm Trees Test; F= Female; M= Male; PCA= Posterior Cortical Atrophy; CBS= Corticobasal Syndrome; SD= Semantic Dementia; NoDiss= no dissociation; P/C<M = significantly lower performance on Purpose and/or Context than on Manipulation; M<P/C= significantly lower performance on Manipulation than on Purpose and/or Context; n.a.= not available.

	Age	**Edu**	**Sex**	**Diagnosis**	**Group**	**MMSE**	**AM**	**Digit Span**	**RAVLT Imm/Del**	**Copy of ROCF**	**Category Fluency**	**Letter Fluency**	**FAB**	**BJLO**	**IMA Right/Left***	**Picture Naming***	**PPT**
G.B.	77	18	F	PCA	NoDiss	27	54	**5**	51/11	29	41	38	17	**18**	71/72	24	49
G.G.	70	6	F	CBS	NoDiss	**24**	44	7	42/9	**8**	36	36	**12**	**16**	**40**/**35**	**23**	44
I.B.	70	8	F	PCA	NoDiss	**21**	**12**	**5**	28/7	**0**	**15**	25	**10**	**0**	**30**/**20**	**15**	44
E.B.	77	11	F	PCA	NoDiss	25	**27**	**5**	31/**4**	**14**	**23**	33	15	**14**	58/**51**	26	48
R.M.	77	5	M	CBS	NoDiss	28	32	6	28/7	**19**	35	27	16	20	58/54	26	46
D.M.	75	5	F	SD	NoDiss	25	45	7	35/5	36	27	28	18	25	65/70	n.a.	49
P.A.	74	18	M	CBS	NoDiss	**23**	36	**5**	29/5	**17**	25	32	**10**	**14**	**36**/**33**	n.a.	n.a.
P.L.	74	7	M	SD	NoDiss	27	52	**5**	45/7	33	**24**	20	15	n.a.	68/67	**11**	43
L.B.	73	8	M	SD	NoDiss	28	54	**5**	n.a.	33	30	21	17	n.a.	70/69	**14**	**40**
A.C.	54	8	F	PCA	NoDiss	**22**	**10**	**4**	**13**/**2**	**2**	**15**	17	**8**	**9**	**32**/**20**	**17**	**25**
S.C.	73	3	F	CBS	NoDiss	27	**30**	**4**	**24**/7	**9**	25	**16**	**12**	n.a.	n.a.	**17**	**38**

	Age	**Edu**	**Sex**	**Diagnosis**	**Group**	**MMSE**	**AM**	**Digit Span**	**RAVLT Imm/Del**	**Copy of ROCF**	**Category Fluency**	**Letter Fluency**	**FAB**	**BJLO**	**IMA Right/Left***	**Picture Naming***	**PPT**
L.G.	70	10	M	CBS	P/C<M M<P/C	**16**	45	**4**	**27**/5	**24**	**14**	**4**	**11**	25	**40/44**	**3**	**29**
E.G.P.	73	13	M	SD	P/C<M	25	49	7	**22/0**	35	**6**	25	17	n.a.	n.a.	**2**	**37**
R.E.	70	8	M	PCA	P/C<M	**22**	38	6	**24/0**	31	**21**	27	17	27	70/67	**9**	**39**
P.V.	70	5	M	SD	P/C<M	29	43	6	36/7	30	26	22	**13**	21	69/63	**11**	**38**
G.B.	78	8	M	SD	P/C<M	**24**	n.a.	9	n.a.	38	**11**	29	n.a.	n.a.	n.a.	**0**	**39**
G.N.	61	5	F	SD	P/C<M	26	50	n.a.	34/7	**27**	**16**	27	n.a.	29	63/61	**4**	**40**
A.U.	57	13	F	SD	P/C<M	**20**	42	**5**	**17/0**	35	**3**	**8**	**7**	28	54/**52**	**2**	**27**
L.A.P.	63	18	M	SD	P/C<M	**23**	35	6	**21/0**	33	**3**	0	n.a.	19	67/68	**1**	**26**
E.C.	81	5	F	CBS	M<P/C	**23**	38	**4**	45/10	**19**	**23**	24	n.a.	**18**	**49/45**	**12**	**33**
F.C.	69	5	M	CBS	M<P/C	**24**	39	**4**	40/8	**10**	**24**	**15**	**11**	**16**	66/54	**20**	**36**
C.C.	62	8	M	PCA	M<P/C	**18**	**17**	**2**	**17**/5	**4**	**17**	**12**	**7**	**7**	**24/17**	**20**	46
C.D.	77	5	F	CBS	M<P/C	26	49	**5**	45/12	**26**	32	22	**9**	**17**	**46/49**	**17**	43
M.R.	70	5	F	PCA	M<P/C	24	21	5	23/6	9	15	20	10	10	47/50	12	n.a.
M.M.	63	8	M	PCA	M<P/C	23	41	3	18/4	10	18	11	13	12	57/49	18	46
P.P.	68	5	M	CBS	M<P/C	19	21	4	42/9	10	31	22	9	n.a.	28/43	15	37

Table 3. Comparison of characteristics of subgroups of patients without dissociations between conditions, with a dissociation favouring Purpose and/or Context over Manipulation (M<P/C), or with a dissociation favouring Manipulation over Purpose/Context (P/C<M). One patient with M<P + C<M dissociations is described in the text. For each subgroup and each demographic or neuropsychological values, mean ± standard deviation are shown. Legend: * = p < 0.01 vs No Dissociation, ** = p < 0.0001 vs No Dissociation, # = p < 0.01 vs M<P/C.

	No Dissociation n. 11	**P/C<M n. 7**	**M<P/C n. 7**
Age	72.2 ±6.5	67.4 ±7.4	70.0 ±6.9
Education	8.8 ±4.9	10.0 ±4.8	6.0 ±1.5
Sex – n. male, female	4, 7	5, 2	4, 3
Context	59.7 ±4.8	43.1 ±6.0*#	60.6 ±3.9
Purpose	62.0 ±5.3	43.3 ±8.3*#	58.7 ±6.2
Manipulation	56.8 ±5.4	42.7 ±8.1**	48.6 ±5.5**
Diagnosis - n. (%):			
- *Semantic dementia*	3 (27.3)	6 (83.3)#	0 (0.0)
- *Corticobasal syndrome*	4 (36.4)	0 (0.0)#	4 (57.1)
- *Posterior cortical atrophy*	4 (36.4)	1 (16.7)	3 (42.9)
Mini Mental State Examination	24.2 ±2.4	23.9 ±2.3	21.1 ±2.7
Attentional Matrices	34.1 ±15.7	44.7 ±4.7	31.0 ±10.9
Digit Span	5.0 ±0.9	6.3 ±1.5#	3.4 ±0.9**
Rey Auditory Verbal Learning Test:			
- *Immediate recall*	28.1 ±11.1	22.5 ±5.1	27.1 ±10.2
- *Delayed recall*	1.4 ±2.6	2.0 ±2.8	5.2 ±2.5
Copy of Rey-Osterrieth Figure	16.4 ±12.7	31.1 ±4.1**#	10.4 ±6.6
Category Fluency	21.6 ±8.7	9.1 ±5.8**	16.6 ±5.6
Letter Fluency	22.3 ±10.8	17.3 ±8.3	12.6 ±3.3
Frontal Assessment Battery	12.7 ±3.1	13.3 ±4.1	9.0 ± 2.3
Benton Judgement of Line Orientation	11.0 ±6.2	22.2 ±3.9**#	10.0 ±3.6
De Renzi's Test of Ideo-Motor Apraxia:			
- *Right limb*	52.8 ±16.5	64.6 ±6.5	45.3 ±14.9
- *Left limb*	49.1 ±20.7	62.2 ±6.4	43.9 ±12.4
Picture Naming	19.2 ±5.6	4.1 ±4.2*#	16.3 ±3.4
Pyramid and Palm Trees	41.7 ±6.9	35.4 ±4.5	39.3 ±5.0

3.3.3 Metabolic neuroimaging findings

Seventeen out of 26 patients who underwent brain FDG-PET suitable for semiquantitative analysis with SPM 8 were included in the metabolic imaging study: patients D.M., E.B., G.B., G.G., I.B., L.B., P.A. and S.C. from the *NoDiss* subgroup, patients A.U., E.G.P., G.B. and P.V. from the *P/C<M* subgroup, and patients C.C., C.D., F.C., M.R. and P.P. from the *M<P/C* subgroup. Patterns of hypometabolism of the three dissociation subgroups (compared with healthy participants) are shown in Figure 2 and anatomical localization of clusters is described in Table 4. There was one area of overlap for the three groups, in the mid-anterior portion of the left middle temporal gyrus. In addition, decreased FDG uptake was evidenced in the polar and ventral regions of the left temporal lobe in *P/C<M* patients, along the dorsolateral surface of the left temporal lobe (from the angular gyrus, through the middle temporal areas, to the inferior temporal cortex) and in the right posterior middle temporal gyrus in *M<P/C* patients, and in the right angular and middle and inferior temporal gyri and bilateral parahippocampal gyri in *NoDiss* patients. When examining hypometabolism patterns of the 17 patients together, without considering the three subgroups, correlation analysis showed that a lower score on the Category Decision task was associated with reduced FDG uptake in the left temporal pole for all three conditions (Figure 3, Table 5). Hypometabolism also involved the anterior fusiform gyrus for both Context and Purpose, and the posterior fusiform for the latter condition, while an additional area of decreased metabolism was evident along the mid portion of the left middle-inferior temporal gyri for Manipulation.

Figure 2. Distribution of hypometabolism in the three subgroups. In green: patients without dissociations between conditions, in blue: patients with a dissociation favoring Manipulation over Purpose and/or Context, in red: patients with a dissociation favoring Purpose and/or Context over Manipulation**.** Clusters are shown at $p < 0.001$ uncorrected and a minimum size of 100 voxels.

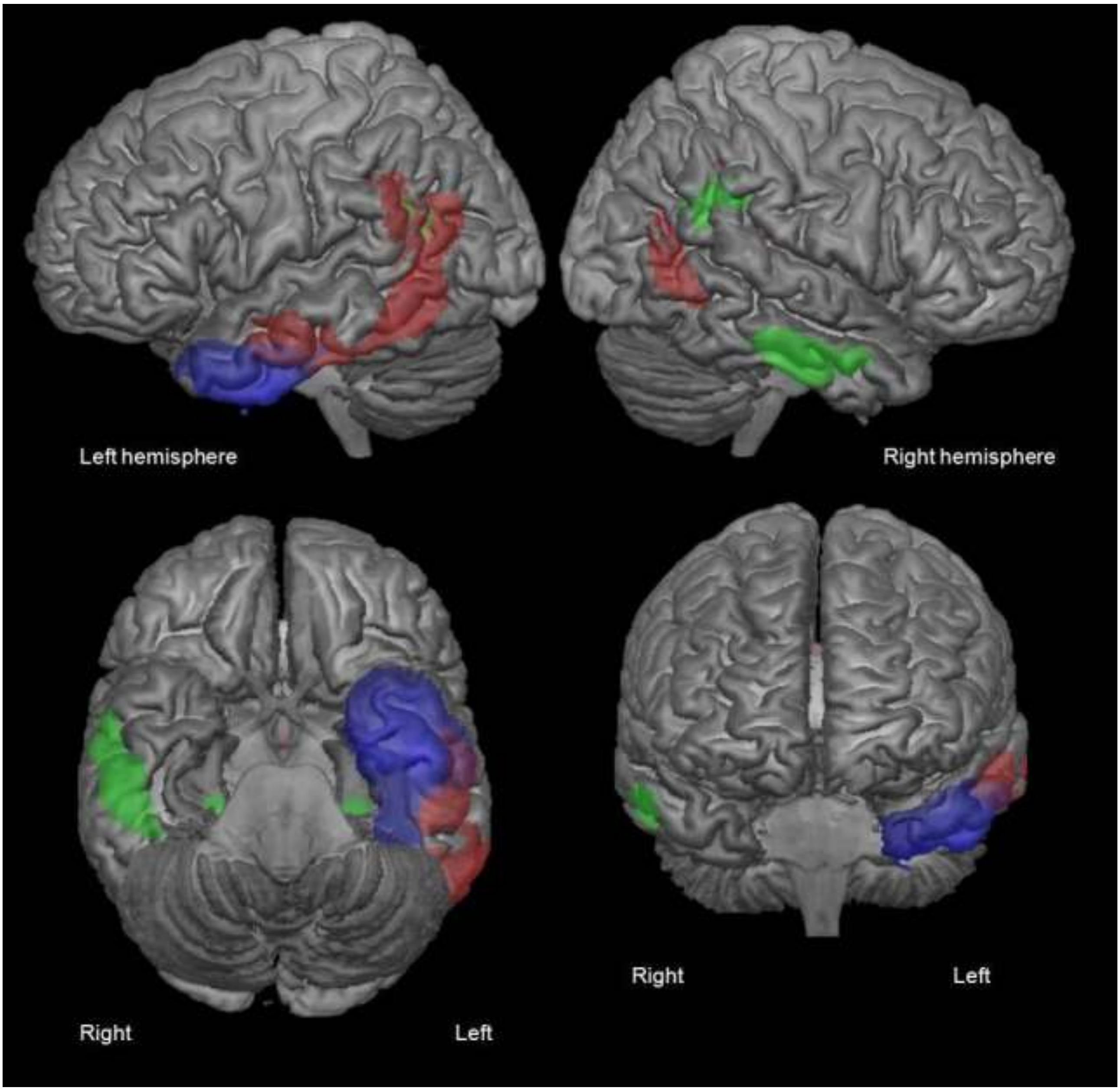


Table 4. Anatomic location of clusters of hypometabolism evidenced in subgroups of patients without dissociations between conditions (No Diss), with a dissociation favoring Purpose and/or Context over Manipulation (M<P/C), or with a dissociation favoring Manipulation over Purpose and/or Context (P/C<M). Legend: MNI= Montreal Neurological Institute template.

	Cluster size	**MNI coordinates**				**Region**
		x	**y**	**z**	**Hemisphere**	**(Brodmann area)**
No Diss	732	60	0	-26	Right	Middle temporal gyrus (21)
		56	-18	-28		Inferior temporal gyrus (20)
	400	42	-52	26	Right	Angular gyrus
	396	-40	-52	20	Left	Middle temporal gyrus
	365	-22	-38	2	Left	Parahippocampal gyrus
	336	22	-36	2	Right	Parahippocampal gyrus
P/C<M	3722	-38	-2	-42	Left	Inferior temporal gyrus (20)
		-40	-34	-22		Fusiform gyrus
		-42	14	-40		Middle temporal gyrus, pole
		-28	16	-38		Superior temporal gyrus, pole
M<P/C	5443	-44	-50	30	Left	Angular gyrus
		-44	-56	0		Middle temporal gyrus
		-60	-6	-20		Middle temporal gyrus (21)
		-64	-58	-10		Inferior temporal gyrus (37)
		-52	-28	-24		Inferior temporal gyrus (20)
		-14	-46	32		Precuneus
		-8	-18	32		Middle cingulate gyrus
		-12	-18	18		Thalamus
	394	44	-62	2	Right	Middle temporal gyrus

Figure 3. Areas of hypometabolism significantly, inversely correlated with performance on the three conditions of the Category Decision task in the 17 patients. From top to bottom: in blue = correlation with performance on Context of use condition, in green = correlation with performance on Purpose condition, in red = correlation with performance on Manipulation condition, all colors together = overlap of all three conditions. Clusters are shown at $p < 0.001$ uncorrected and a minimum size of 100 voxels, and were all located in the left hemisphere.

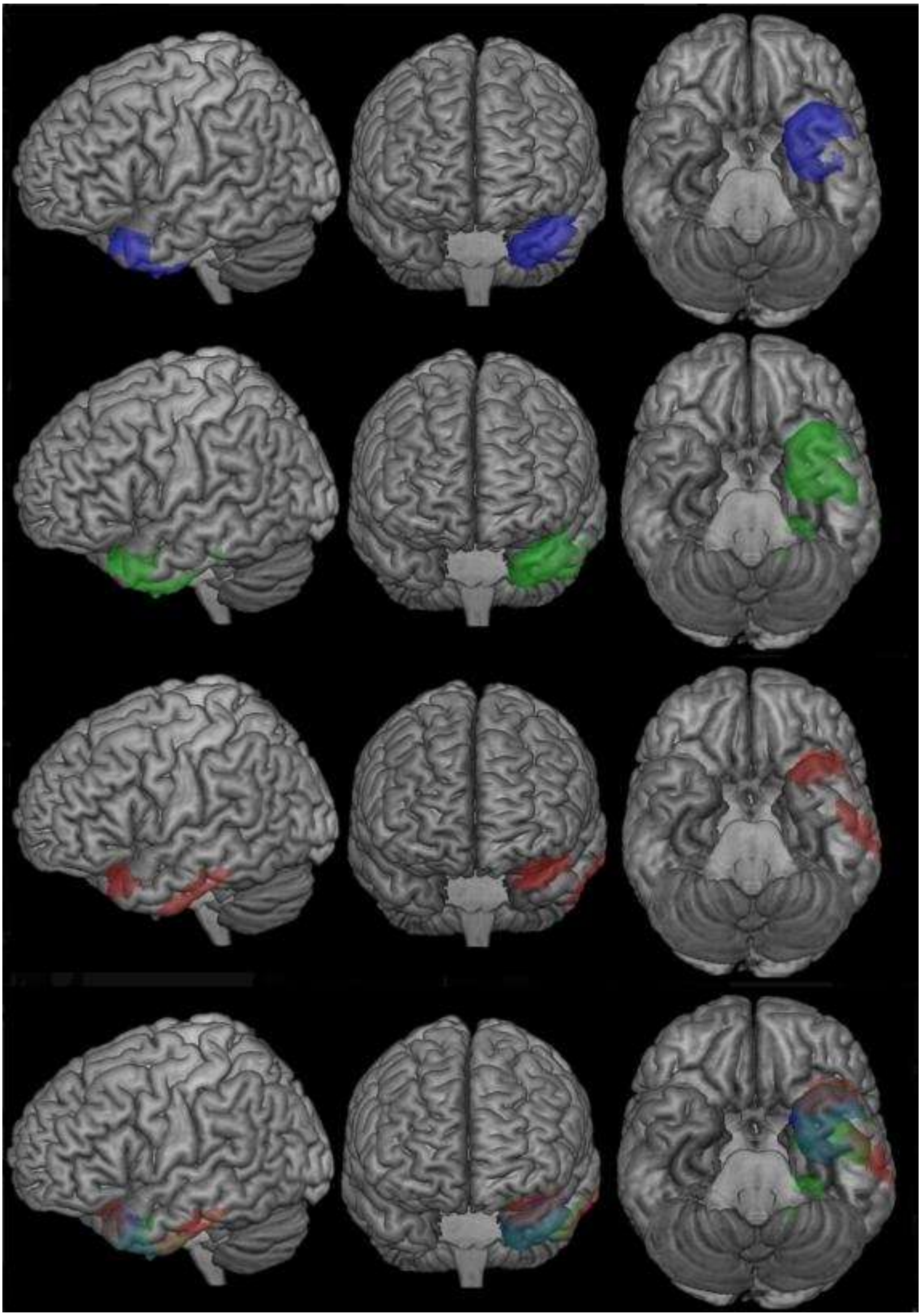


Table 5. Anatomic location of clusters of hypometabolism correlated with performance on the three conditions of the Category Decision task. Legend: MNI= Montreal Neurological Institute template.

	Cluster size	**MNI coordinates x**	**y**	**z**	**Hemisphere**	**Region (Brodmann area)**
Context	1970	-40	22	-20	Left	Superior temporal gyrus, pole (38)
		-50	-8	-40		Inferior temporal gyrus (20)
		-22	-6	-46		Fusiform gyrus
Purpose	2907	-32	28	-32	Left	Superior temporal gyrus, pole
		-64	-24	-20		Inferior temporal gyrus (20)
		-44	24	-26		Superior temporal gyrus, pole (38)
		-34	10	-44		Middle temporal gyrus, pole (38)
		-22	-8	-40		Fusiform gyrus
	707	-26	-40	-18	Left	Fusiform gyrus (37)
Manipulation	811	-32	26	-28	Left	Superior temporal gyrus, pole
		-56	10	-24		Middle temporal gyrus, pole (21)
	766	-64	-24	-20	Left	Inferior temporal gyrus (20)
		-66	-18	-18		Middle temporal gyrus (21)

3.4 DISCUSSION

In recent literature the way in which different types of object knowledge, such as information about how to manipulate an object, for which purpose it is used and in which context, are represented in the brain is still debated (see paragraphs 1.3.1 and 3.1). According to the strong version of the embodied cognition (Gallese & Lakoff, 2005), action shapes our semantic knowledge about objects. When premotor and motor areas are damaged, action knowledge about how to use an object, in which context and for which purpose is disrupted, causing an impoverishment of the corresponding object concept. Another recent hypothesis (Martin, 2016), still enclosed in the embodied framework, claims that object semantic knowledge is not stored in primary sensory and motor areas, but all sensory- and motor-related features of objects are integrated in multi-modal convergence areas. This means that a particular object property (e.g. the color), derived from a specific sensory or motor modality (e.g. vision), may be disrupted causing difficulties in associating objects on the basis of that property, but the individual may still be able to associate objects on the basis of other semantic features. Conversely, when multi-modal convergence zones are damaged, the object knowledge deficit may involve different modalities and be observed in various semantic tasks. However, since multi-modal convergence zones are highly interconnected with neighboring areas, it is unlikely that object concepts might be impaired as a whole (Mahon et al., 2007; Beauchamp & Martin, 2007; Campanella et al., 2010). This means that, depending on the lesion spread and on the neural connectivity that is disrupted, one modality may be significantly more affected than others, and thus a more severe deficit for a specific semantic feature may be observed depending on the context and the task. Conversely, according to the Hub and Spokes theory (Patterson et al., 2007; Lambon-Ralph et al., 2010), the different types of object knowledge, derived from various sensory and motor modality-specific areas, converge in the bilateral anterior temporal lobes (ATLs) building supra-modal, rather than multi-modal, concepts. This means that a lesion at this level provoke an equal deficit for any type of object knowledge that is investigated, and for any task that is proposed to the patient. The present study aimed at exploring whether predictions of these three theoretical models could be disconfirmed, or not, by analyzing patterns of performance and associated neural lesions in a sample of patients with various types of dementia, who were asked to decide whether two words referred to objects sharing the same Manipulation, Purpose, or Context of use. Patients were selected if they had semantic difficulties and/or motor control deficits (i.e. Ideo-Motor apraxia, see paragraph 3.2.1). Single-case analysis with Crawford's method was conducted to detect dissociated patterns of performance on the three types of semantic association. Results revealed that Manipulation, Purpose and Context of Use could be differentially damaged in patients, enabling to identify three distinct patterns of behavior (see paragraph 3.3.1). A first group of patients (*No Diss*) was homogeneously impaired on the three conditions, and thus did not satisfy Crawford's criteria for a dissociation. A second group (*M < P/C*) showed a predominant deficit in the Manipulation condition, with relatively spared performance on Context of Use and/or Purpose. Criteria for *Classical* dissociations, indicating a selective deficit of Manipulation, relative to Purpose and/or Context, were satisfied in three patients. This pattern suggests that Manipulation knowledge may be selectively impaired, and may still be able to associate objects according to other semantic features (Purpose or Context of Use). This result is in contrast with the strong version of the embodied cognition, which states that action knowledge is necessary for the integrity of object concepts and object semantics, while it is in agreement with models that hypothesize a semantic architecture that includes both modality-specific (selective semantic deficits) and multi-modal/supra-modal impairment. A third pattern of behavior (*P/C < M*) consisted of impaired Purpose, Context of Use and Manipulation, but with the latter significantly better performed than at least one of the other two conditions (*Strong* dissociations). Furthermore, while criteria for a *Classical* dissociation favoring Purpose over Context were matched in one case of the *No Diss* group (I.B.), the reverse *Classical* dissociation (P < C) was not detected in any other patient (although some cases showed a significantly lower z-score than healthy participants in Purpose, but not in Context). In other words, despite a major impairment on Purpose condition, patients with severely poor performance on Purpose were defective also on Manipulation and Context. Analysis of clinical and neuropsychological profiles for the three patient subgroups (see paragraph 3.3.2) revealed that patients with selective deficit of Manipulation had predominant diagnosis of corticobasal syndrome (CBS) or posterior cortical atrophy (PCA) and had a significantly affected performance on the Digit span, when compared to the *NoDiss* subgroup, and on the copy of the complex figure and the line orientation judgement tests in comparison to the *P/C < M* subgroup. Ideo-Motor apraxia had no impact in determining subgroups differences on Manipulation. Furthermore, patterns of hypometabolism in this group (see paragraph 3.3.3, Figure 2 and Table 4) included areas of the left posterior (e.g. the pMTG), inferior and middle temporal cortex, and of the left inferior parietal cortex (e.g. the angular gyrus). The lack of significant hypometabolism in premotor or motor areas is in great contrast with the strong view of the embodied perspective. Conversely, these findings are in agreement with a recent study (Kalénine & Buxbaum, 2016) indicating that lesions of the left posterior temporal cortex were associated with poor performance on a spoken verb-to-seen gesture matching task (i.e. a measure of action knowledge) and poor performance on a semantic association task requiring to match objects that were used together to perform an action (e.g. axe and wood). According to the authors, the left posterior temporal cortex is the neural locus for stored representation of the actions that are typically associated with objects, i.e. knowledge about objects manipulation. In a previous study conducted by the same group (Kalénine et al., 2010), this area was also significantly associated with gestures recognition, which is assumed to rely upon access to manipulation knowledge (Rothi et al., 1991; Cubelli et al., 2000). Moreover, a recent functional Magnetic Resonance Imaging (fMRI) study investigated neural correlates in healthy participants while they had to decide whether a word referred to something that could be experienced through the senses (Fernandino et al., 2015). Words used in the study could refer to different object attributes, including manipulation, which was highly correlated with activity in the pMTG and the lateral occipito-temporal cortex. Thus, our findings on patients with deficit on Manipulation knowledge are in agreement with current literature on the topic. The *P/C < M* subgroup, instead, included a majority of patients with SD and only one patient with PCA, who had a predominant lexical-semantic deficit at onset. Performance of these patients, relative to the other two subgroups, was significantly lower on Category Fluency and Picture naming, but significantly better on line orientation judgment and on the copy of a complex figure (see paragraph 3.3.2). Moreover, patients who had severe lexical abilities deficits (cases G.N., A.U., L.A.P. and also L.G.), as revealed by Semantic Fluency and Picture naming scores, had also the lowest z-scores for Purpose performance (G.N. = -17.1; A.U. = -18.4; L.A.P. = -23.4; L.G. = -19.0). Neuroimaging analysis on the *P/C < M* subgroup (see paragraph 3.3.3, Figure 2 and Table 4) showed that these patients had predominant hypometabolism in the left anterior temporal lobe and particularly in the temporal pole, which is usually damaged in SD patients (Gorno-Tempini et al., 2011). Patients enclosed in the *NoDiss* group, instead, showed predominant patterns of hypometabolism in the right hemisphere (see paragraph 3.3.3, Figure 2 and Table 4). However, when considering the whole group of 17 patients (Figure 3 and Table 5), areas of hypometabolism correlated with the three semantic conditions, overlapped in the left anterior temporal lobe, and especially in the temporal pole. Taken together, behavioral and metabolic neuroimaging findings suggest that the three types of semantic categorization investigated in the study may be selectively (as revealed by *Classical* dissociations) or disproportionately (as revealed by *Strong* dissociations) impaired, and are, at least partially, supported by different neural regions. A selective or predominant deficit for Manipulation knowledge was associated with damage to left posterior temporal areas, including the pMTG and the inferior temporal gyrus, while predominant deficit in categorizing objects according to Purpose and/or Context of use was associated with hypometabolism in more anterior temporal regions of the left hemisphere, including the middle and inferior temporal gyri and the temporal pole. These results are hardly interpretable within a strong embodiment cognition framework, which posits that primary sensory and motor areas are the neural underpinnings of both manipulation knowledge and object semantic representations. Our findings are in line with theories hypothesizing that object concepts result from the combination of different object features, represented separately in the brain, and converging in either multi-modal or supra-modal areas. Moreover, even in patients with

SD and severe semantic impairment, it was possible to detect dissociated patterns of impairment, suggesting that even when a multi-modal convergence zone is damaged, one specific modality may be significantly more affected than others. Interestingly, it was not possible to detect *Classical* dissociations in terms of spared performance on Context or Manipulation conditions but defective performance on Purpose condition. One possible explanation is that object features that are engaged in the Purpose condition of our Category Decision task play a crucial role in objects representation. Indeed, some authors argued that functional properties allow the discrimination between different categories of manipulable objects – e.g. a pair of scissors and a knife are objects to cut whereas a garden shovel and a spade are objects to dig (Shallice, 1988; Warrington & Shallice, 1984). This means that when functional properties of objects are damaged, it is difficult to access knowledge about what the object is for and how it is used or manipulated. Accordingly, two neuroimaging studies on healthy participants investigating neural activation during a semantic judgement task on the basis of manipulation or function properties of objects found no specific activations in the function – manipulation contrast (Kellenbach et al., 2003; Boronat et al., 2005). This may suggest that retrieving of manipulation requires retrieving of function (Leshinskaya & Caramazza, 2015). Alternatively, a lack of spared performance on Manipulation or Context of Use conditions when Purpose was affected may be interpreted within the Hub and Spokes framework (Patterson et al., 2007; Lambon-Ralph et al., 2010). In fact, the dissociation $P/C < M$ was detected especially in patients with SD and ATL damage. This may indicate that when damage to the ATL occurs, patients' performance becomes severely damaged for all objects features. In fact, performance on the Manipulation condition of the $P/C < M$ subgroup was as impaired as that of the $M < P/C$ subgroup, indicating a severe impairment of SD patients also in the Manipulation condition. Furthermore, when considering all patients, irrespective of the three subgroups, poor performance in any of the three semantic conditions significantly correlated with hypometabolism in the ATL. To sum up, results of the present study are in contrast with a strong interpretation of the embodied theories, while they are compatible with both theoretical accounts for multi-modal object representations and the Hub and Spokes theory. One limitation of the present study is that not all patients that were tested could be included also in the neuroimaging analysis. Thus, metabolic neuroimaging results are not representative of the whole sample, and single-case idiosyncrasies and/or more severely impaired patients may have influenced the group tendency. Furthermore, since performance on Manipulation condition in the $P/C < M$ subgroup was comparable to that obtained by the $M < P/C$ subgroup, neural correlates of Purpose may be partially masked by areas of hypometabolism correlated with poor performance on Manipulation. A larger sample size may help in going beyond these limitations. Overall, this experiment demonstrates that different types of object knowledge are stored in distinct brain areas in the left hemisphere, and may be selectively impaired in neurodegenerative patients. Specifically, poor performance in identifying a semantic relationship based on manipulation was detected in patients with lesions encompassing the angular gyrus, the inferior temporal cortex and the middle temporal gyrus in the left hemisphere. These regions were found, in previous studies, to support also gesture recognition (Kalénine et al., 2010), the ability to associate objects that are used together in the same action, and the ability to associate an action verb to the corresponding gesture with an object (Kalénine & Buxbaum, 2016). Thus, the neural areas supporting manipulation knowledge may overlap with stored representation of known actions that are typically associated with objects. For this reason, manipulation knowledge may be crucial, especially when we need to use objects in the everyday life. The third experiment of the present work focuses on the relationship between manipulation knowledge and actual object use.

CHAPTER 4. STUDY 3: HOW WE INTERACT WITH TOOLS? THE RELATIONSHIP BETWEEN SEMANTICS AND PRAXIS

4.1 INTRODUCTION

In the second experiment of the present work, we found that knowledge about how an object can be manipulated may be selectively impaired in patients with lesions encompassing areas of the inferior parietal lobe, the inferior temporal cortex and the middle temporal gyrus of the left hemisphere. These areas have been reported to support also action recognition, action knowledge and object use. Thus, in the present study we focused on the relationship between manipulation knowledge and object use. Human ability to use tools in everyday life is thought to rely upon distinct cognitive processes, such as formulation of action intentions, access to tool semantic knowledge, correct action planning and action control, and finally action execution (Thill et al., 2013; van Elk et al., 2014). The relationship between tool use and each of these components is still at odds in current research on the topic. A first issue concerns the contribution of tool semantic knowledge in tool use. Studies on patients with Semantic Dementia (SD), a neurodegenerative disorder characterized by loss of words and objects meaning due to anterior temporal lobes atrophy (Gorno-Tempini et al., 2011), showed that these patients were impaired both in actual object use and in semantic object knowledge (Hodges et al., 2000; Bozeat et al., 2002; Coccia et al., 2004). Furthermore, the severity of the semantic deficit was found to significantly predict patients' residual abilities to use objects (Silveri & Ciccarelli, 2009). These results suggest the existence of a strict link between semantics and object use, in agreement with theoretical models positing common cognitive mechanisms between object conceptual knowledge and object use (e.g. the Hub and spokes theory, Patterson et al., 2007, see paragraph 1.3.1). However, other studies showed that patients with SD had spared object use although they retained little linguistic and semantic knowledge (Buxbaum et al., 1997; Lauro-Grotto et al., 1997) even for those objects whose semantic meaning was lost (Negri et al., 2007a). According to another theoretical framework, object semantic knowledge is constituted by various types of information highly distributed in the cortex, so that only part of it may have a role in object use (Buxbaum & Saffran, 2002; Binkofski & Buxbaum, 2013). In this framework, it was proposed that the cognitive bases of object use can be organized into at least three types of knowledge, which can also be associated to distinct brain regions: function knowledge, manipulation knowledge (Boronat et al., 2005; Canessa et al., 2008; Kalénine et al., 2010), and sensory (e.g. visual and tactile) structural representations (Rothi et al., 1991; Cubelli et al., 2000). This theoretical framework has recently been called manipulation-based approach (Osiurak & Badets, 2016). The term 'function knowledge' is used not only to indicate the semantic long-term information about the purpose of an action performed with an object, but also to include its context of use (Buxbaum, 2001; Martin & Chao, 2001). This functional/contextual knowledge is represented in numerous left hemisphere regions including the frontal and prefrontal cortex, the inferior parietal lobule (IPL) and areas belonging to the ventral visual system for object recognition (Boronat et al., 2005; Canessa et al., 2008). Manipulation knowledge refers to sensorimotor knowledge about the way in which an object is manipulated, i.e. the appropriate gesture to use it. Liepmann (1905) suggested that the left hemisphere contains the motor engrams, which consist of space-time memories that control purposeful skilled movements. Thus, the semantic system would process the output of various sensory, motor and proprioceptive gesture systems to derive knowledge about tool manipulation, which is stored in the left inferior parietal lobe (Buxbaum, 2001). Finally, the representation of an action, derived from this type of semantic information, has to be translated into the appropriate motor program to perform the action with an object. At this processing level, structural representations of the appropriate gesture have a crucial role. The cognitive system that is assumed to control action execution is the dorsal action system (Binkofski & Buxbaum, 2013). Recently, it has been proposed that manipulation knowledge is represented within the ventro-dorsal system and that the posterior part of the middle temporal gyrus has a crucial role in integrating gestural with other semantic information (Kalénine et al, 2010). While manipulation knowledge contains information about gestures with familiar tools, structural representations support the processing of meaningless gestures and manipulation of new, unknown, tools. Distinct brain pathways for meaningful and meaningless gestures were reported in a meta-analysis of functional Magnetic Resonance Imaging (fMRI)/Positron Emission Tomography (PET) studies (Niessen et al., 2014) and in a Voxel-Based Lesion-Symptom Mapping (VBLSM) study (Hoeren et al., 2014). In this framework, function and manipulation knowledge are differentially represented at a conceptual level and may support tool use independently, thereby suggesting that an intact function knowledge may partially compensate for a manipulation knowledge deficit, and vice-versa (Buxbaum, 2001; Buxbaum & Saffran, 2002; van Elk et al., 2014). This is also in agreement with theories assuming that distinct visual routes have different roles in action, but strongly interact with each other (Phillips et al., 2002; Rumiati et al., 2005). A first route allows the extraction of relevant visual features of objects to form a structural description of it, while a second route processes the relevant semantic properties of objects. For example, damage of the former route may cause an impairment when trying to retrieve the relevant motor and sensory properties of an object to correctly use it, but the latter route may provide important semantic information about the object functional properties, allowing subjects to correctly use it in a purposeful manner. In contrast to the manipulation-based approach, the technical-reasoning hypothesis (Osiurak et al., 2010) assumes that the use of both familiar and novel tools is made possible by reasoning on the relevant mechanical properties of tools and objects, rather than by accessing to manipulation knowledge. In this view, mechanical knowledge is used to form a mental simulation of the action with a certain tool, and the act of reasoning is likely to rely on the activity of the left inferior parietal lobule (Goldenberg et al., 2007). Following this account, function knowledge is not involved in mechanical transformations, but organizes the search in long-term memory to get information on tools or objects that are not at hand within the workspace. As a consequence, no compensation of function on mechanical knowledge would be possible during actual object use (Osiurak & Badets, 2016). A recent study (Baumard et al., 2016) tried to compare manipulation-based approach and technical reasoning hypothesis predictions by investigating the relationship between semantic knowledge about object function/context of use, actual tool use abilities and mechanical problem solving (MPS) in patients with Semantic Dementia (SD), Corticobasal syndrome (CBS) and Alzheimer's Disease (AD). The authors included tests that allowed the evaluation of pantomime of object use, single object use, and tool-recipient action execution (which was thought to be the most reliable measure for everyday object use impairment). The functional/context of use knowledge task required patients to associate a probe object picture (e.g. scissors) with another object picture sharing the same function (e.g. knife) or with the picture of the appropriate context of use of the object (e.g. haircutter). The single object use task required patients to show how to use an object alone (e.g. a hammer), whereas in the tool-recipient task the object had to be employed with the corresponding recipient (e.g. the patient had to punch a nail with the hammer). In strong contrast to the manipulation-based approach, results on CBS patients revealed severe impairment in the MPS task and in the tool use tasks, but not in the functional/context of use association task, suggesting that function knowledge was not necessary to accurately use tools. Conversely, SD patients had an equal impairment of both functional/context of use associations and object use abilities, but obtained a relatively spared performance on the MPS task. These results were compatible with the manipulation-based approach. Finally, results on AD patients were partially in contrast with both theories. Patients showed different patterns of dissociation between performance on MPS, functional/context of use associations and tool use deficits. In addition, some cases exhibited tool use disorders without either loss of semantic knowledge or problem solving deficits. One limitation of Baumard and colleagues study (2016) is that it did not include a manipulation knowledge task. Thus, the core difference between the two theoretical frameworks, that is the existence of stored knowledge about the specific gestures that we can do with tools, remains unexplored. In the present study, the principal aim was to investigate the role of manipulation and function knowledge when patients were required to use single objects or multiple objects for a specific purpose. In current literature, there are a few standardized tests for objects use (e.g., Zanini et al. 1999, Negri et al. 2007b, Bartolo et al. 2008). However, these tests have some relevant limitations such as lack of normative or patients data. In fact, up to date no object use test provides both normative and patient data. Furthermore, some of these single object use tasks have the problem that healthy participants perform at ceiling, so that even 1 potential error would correspond to defective performance. With the aim to address these methodological limitations, a new task assessing the use of single objects was specifically designed for the present study, taking inspiration from another published test (Negri et al. 2007b). Similarly, some tasks testing for the ability to perform complex actions are reported in literature. However, the most famous test for ideational apraxia, created by De Renzi & Lucchelli (1988), has no quantitative cut off, while three other tests (Goldenberg & Spatt, 2009, Bickerton et al., 2012; Buchmann & Randerath, 2017) require to perform actions with only two objects (not more) and that are usually executed with two hands (e.g. to punch two sheets of paper with a stapler). This latter issue is especially a problem for stroke patients with hemiparesis and leaves some problems to the experimenter who has to evaluate if the action is correctly executed. Thus, a new multiple object use task was ideated for the present study, as well as a Manipulation/Function semantic association task. Besides the debate on the role of semantic knowledge in tool use, another open question regards the relationship between tool use disorders and the ability to correctly execute meaningless gestures. To date, in fact, many studies focused on the relationship between meaningful and meaningless gestures (Goldenberg & Hagmann, 1997; Bartolo et al., 2001; Rumiati & Tessari, 2002; Rumiati et al., 2005; Goldenberg & Karnath, 2006; Tessari et al., 2007; Mengotti et al., 2013; Achilles et al., 2016) or between different types of meaningful and tool-related gestures (Vry et al., 2014; Hermsdörfer et al., 2013; Martin et al., 2016; Dressing et al., 2016), while few studies tried to investigate the role of visuo-motor processes in actual object use (Buxbaum et al., 2014). Furthermore, results on CBS patients in Baumard and colleagues' study (2016), may indicate that an impairment of the visuo-motor processes involved in the imitation of meaningless gestures have an impact on object use abilities. Thus, the present study included also a meaningless gestures imitation task. Another distinction between the two theoretical perspectives is the different prediction about tool use and tool grasping deficits. According to the manipulation based approach, the grasp of an object is an online process, because it is executed under control of vision, and is supported by the dorso-dorsal stream, whereas the use of an object is an offline process, made possible through access to stored knowledge supported by the ventro-dorsal stream (Binkofski & Buxbaum, 2013). This means that a patient could be able to correctly grasp a tool, albeit not being able to use it. According to the technical reasoning hypothesis, instead, both grasp and use of an object are mainly guided by the mental simulation of the mechanical action via online perceptual control. Consequently, grasp and use deficits should co-occur. To address this issue, the single object use task included two separate scores for Grasp and Use. To sum up, the aim of the present study was to investigate whether manipulation-based approach or technical reasoning hypothesis predictions were satisfied or disconfirmed. Since the most intriguing result in Baumard et al.'s study (2016) was on AD patients, the present study investigated performance on a Manipulation/Function task, a general semantic association task, two object use tasks (single object use and multiple object use) and different apraxia tasks (including a test for meaningless gestures only) in this patient population. Following the manipulation-based approach, it is expected to find significant positive correlations between performance on the Manipulation/Function task and the two object use tasks. Furthermore, intact access to object function knowledge and the final purpose of the action may compensate for a manipulation knowledge deficit, providing a clue as to the correct use of the object. Conversely, a lack of correlation between performance on the Manipulation/Function task and the object use tasks would be against this hypothesis. Specifically, if manipulation knowledge is damaged, but performance on the two object use tasks is spared, predictions made by the manipulation-based approach would be disconfirmed and another cognitive mechanism (such as technical reasoning) should be taken into account. Second, according to the manipulation-based approach, grasp and use may dissociate, and thus it is expected that, even for the same object, a patient could be able to grasp it but not to use it correctly. Third, the study aims at exploring the relationship between presence of apraxic symptoms, and especially damage to the visuo-motor processes employed in meaningless gestures execution, and object use performance.

4.2 MATERIALS AND METHODS

4.2.1 Participants

The present study was conducted in collaboration with the University Clinic of Cologne (Germany). First, a sample of 29 German healthy participants (Age: 69.5 ± 7.5; Education: 20.9 ± 16.4; Gender: 15 men, 14 women) was recruited at the University Clinic of Cologne and tested with the experimental battery in order to remove potentially problematic items and define the final version of the tasks. Items selection procedure for each experimental task is reported in paragraph 4.2.3. Twenty-one Italian patients with probable diagnosis of AD (Age: 75.4 ± 4.3; Education: 7.9 ± 3.3; Gender: 10 men, 11women) and 20 Italian healthy participants (Age: 73.6 ± 10.5; Education: 10.9 ± 5.0 Gender: 7 men, 13 women) took part in the Italian study. All participants were included only if they were right handed, as measured by the Oldfield Laterality Quotient (LQ; Oldfield, 1971). Healthy participants were included if they had a normal performance on the MMSE (according to German and Italian normative cutoff scores) and no previous psychiatric or neurologic history. Italian patients were recruited at the Evaluation Unit of Alzheimer’s Disease of San Gerardo Hospital in Monza and conducted a neuropsychological battery that included the Mini-Mental State Examination (MMSE, Measso et al., 1993), a short-term verbal memory task (Digit Span, Monaco et al., 2013), a verbal learning task on semantically related words (VLT, Mauri et al., 1997), which included also a recognition task, language testing (Letter and Category fluencies, Costa et al., 2014; Word and Sentence Comprehension subtests of the Neuropsychological Examination for Aphasia, Capasso & Miceli, 2001), and a battery for frontal syndrome (Frontal Assessment Battery (FAB), Appollonio et al., 2005). According to current International Working Group criteria for probable diagnosis of typical AD (Dubois et al., 2014), patients were included if they referred progressive change in memory function over more than 6 months, had long-term memory deficits that could not be compensated in a cued recall (e.g. the recognition task), and had significant hypometabolism in temporal and temporo-parietal areas, and especially hippocampus and medial temporal areas, at 18F-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET). Exclusion criteria were presence of other illnesses, such as cerebrovascular diseases, major depression, or metabolic disease, presence of extrapyramidal signs, gait disturbances, or prevalent behavioral changes. A description of demographic and neuropsychological characteristics of all patients is depicted in Table 1.

Table 1. Demographic, clinical and neuropsychological features of AD patients. Legend: Gen = Gender, Edu = Education, MMSE = MiniMental State Examination, WC = Word Comprehension, SC = Sentence Comprehension, LettFlu = Letter Fluency, SemFlu = Semantic Fluency, VLT_i = immediate recall of the Verbal Learning Task, VLT_d = delayed recall of the Verbal Learning Task, VLT_r = recognition of the Verbal Learning Task, FAB = Frontal Assessment Battery, m = man, w = woman. Cut-off scores: MMSE ≥ 23.8; WC ≥ 18.4; SC ≥ 11.6; Span ≥ 4.3; LettFlu ≥ 17.78; SemFlu ≥ 28.34; VLT_i ≥ 27.9; VLT_d ≥ 4.8; VLT_r ≥ 22.6; FAB ≥ 13.5. In bold: values below the cut-off. Underlined scores: scores at a borderline level. n.a. = not available. ** = severe dysarthria and effortless speech.

Case	Gen	Edu	Age	MMSE	WC	SC	Span	LettFlu	SemFlu	VLT_i	VLT_d	VLT_r	FAB
LB	m	5	74	29.0	20.0	13.5	6.7	28.4	38.1	30.8	**3.9**	**13.7**	13.5
PV	m	5	73	28.0	18.4	**11.5**	5.5	26.6	**28.1**	n.a.°	n.a.°	n.a.	**13.3**
FP	w	5	79	**23.0**	19.6	12.7	4.8	25.4	37.7	30.0	**0.0**	25.0	**12.8**
GP	w	12	80	**18.9**	19.4	14.0	4.4	30.5	**21.9**	**17.5**	**1.9**	**16.5**	**11.5**
GE	m	5	79	25.0	20.0	13.7	5.8	25.4	36.1	**26.9**	6.5	25	**12.9**
GB	m	8	78	24.2	**16.1**	13.5	9.7	29.0	**11.0**	n.a.°°	n.a.°°	n.a.°°	n.a.°°
AC	w	5	69	**23.2**	18.4	12.5	5.0	33.4	32.7	n.a.°°	n.a.°°	n.a.°°	n.a.°°
CC	m	13	77	24.9	n.a.	n.a.	6.3	**11.5**	**26.3**	31.4	**2.3**	23.2	**12.2**
MP	w	8	77	25.2	19.6	14.0	4.5	20.7	31.9	31.6	**2.4**	**22.0**	13.9
MG	w	13	78	24.9	18.6	13.2	6.4	24.5	33.9	**23.5**	**2.9**	**22.5**	13.5
FPA	m	8	72	24.2	20.0	13.3	6.4	32.9	30.3	**21.6**	**0.0**	**19.7**	15.7
GR	m	13	77	24.9	18.6	13.2	5.8	28.5	53.3	34.4	**4.3**	26.2	**13.2**
TC	w	3	70	**14.2**	18.4	**8.3**	**3.0**	**1****	n.a.**	**2****	n.a.**	n.a.**	n.a.
AF	w	5	77	**18.0**	**17.6**	11.7	5.7	24.4	30.7	33.9	**3.0**	**16.7**	**12.5**
ACA	w	8	84	**23.2**	**17.6**	13.5	5.9	19.7	**21.9**	**18.9**	**0.0**	**21.7**	13.7
MM	m	10	74	**20.9**	20.0	14.0	6.5	26.7	38.3	**23.5**	5.0	**4.3**	**12.9**
RB	w	5	81	**19.0**	18.6	13.7	4.8	**17.4**	31.7	**25.0**	**0.0**	**18.0**	**10.9**
IS	w	8	69	**23.5**	**17.4**	13.3	5.4	46.9	30.9	**13.7**	**0.0**	**16.7**	13.7
NM	m	13	71	28.9	20.0	14.0	5.1	18.6	35.3	30.5	**3.8**	27.0	15.9
GPA	w	8	69	25.2	18.4	14.0	6.4	28.9	30.9	**26.7**	**0.0**	**20.7**	15.7
ACI	m	5	75	**19.0**	20.0	14.0	5.7	30.4	32.1	28.8	**0.0**	**18.7**	15.5

° This patient was tested with another test for verbal short-term and long-term memory (short story recall [December, 6th]; Carlesimo et al., 2002), in which he scored 0 points in both the immediate and delayed recall. °° Data on these tests are not available, but patients conducted an extensive battery for another study which revealed major memory deficits.

4.2.3 Assessment of Apraxia

To test for presence/absence of Ideo-Motor apraxia, the Goldenberg Imitation Test (GIT) for hand and finger gestures was included (Goldenberg, 2001). This test investigates performance on meaningless gestures only, testing for damage to the visuo-motor route for gestures execution. Both the Hand and Finger subscales include 10 gestures. Two points are assigned for correct imitation at first presentation, with a maximum score of 20 points for each subscale. If the participant was not able to correctly perform the gesture at first presentation, the experimenter showed the gesture once again. A correct imitation on second presentation was scored 1 point, whereas 0 points were assigned if the gesture was still wrong. The German cut-off scores were 18 and 17 points, for the hand and finger subscales, respectively. In addition, an extensive battery for oral and upper limb apraxia (Cologne Apraxia Screening (CAS), Wirth et al., 2016) was included to test also for pantomime of object use and imitation of meaningful and meaningless gestures. The maximum total score for the battery is 80, with cut-off set at 77 points. Of particular interest for the present study are the Pantomime of Object Use subscale for the upper limb (POU_L), and imitation of meaningless and meaningful gestures for the upper limb (IML). The POU_L subtest required participants to execute the specific movements associated with 5 objects (hand whisk, game dice, lighter, spinning top, scissors) presented as black-and-white pictures. For each object, two or three movements were required to successfully complete the gesture (e.g. the game dice require to partially close the hand and make a rapid movement to launch the dice). Each movement was evaluated 2 or 1 point, so that 4 points could be obtained for each item, with a maximum of 20 points (4 x 5) for the POU_L subscale. Evaluation of the two meaningless and the three meaningful gestures of the IML subscale was, again, on picture presentation of the gesture to be imitated (the participant was presented with a photo of the gesture performed by a girl). The experimenter was allowed to present the visual stimulus a second time if the participant failed at first presentation. Four points were assigned for correct imitation at first presentation, 2 points were assigned for correct imitation at second presentation, and 0 points were assigned if the gesture was wrong again after the second presentation. The total score for the IML subscale was 20 points (IML = 2 meaningful gestures x 4 points + 3 meaningless gestures x 4 points). The CAS was developed in two parallel versions, one for gestures to be executed with the right hand and one for gestures to be executed with the left hand.

4.2.3 Experimental tasks

All tasks were constructed at the University Clinic of Cologne (Germany) and first applied on a sample of 29 German healthy participants. For every task, items that could not be correctly performed by at least 70 percent of healthy participants were excluded. As regards the two Object Use tasks, half of healthy participants performed each action with the dominant right hand, while the other half of participants performed each action with the left non-dominant hand. This decision was made in order to take into account possible differences when using the non-dominant hand, since the Object Use tasks were developed to be applied also on stroke hemiparetic patients.

4.2.3.1 Single Object Use task (SOU)

In order to have a suitable task for hemiparetic stroke patients and to facilitate the evaluation of the action made by the experimenter, all the objects could be used with one hand only. The first version of the SOU task included 25 common objects, but 2 items were subsequently discharged (i.e. the lemon squeezer and the book) because they were performed with two hands by most of German healthy participants. The final version of the task included the following 23 objects: duster, eraser, fork, gun, hammer, iron, jug, key, knife, ladle, light bulb, pencil, cake spatula, saw, screwdriver, table tennis racket, roll paintbrush, rattle, hairbrush, ice scraper, shovel, remote control, hand bell. Each object was placed, one at each time, on a plastic panel in front of the subject, along his body midline. Objects that had a specific handle to be grasped were placed with the handle oriented toward the participant, in order to facilitate grasping and not require any mental rotation operation. The light bulb was placed with the glass part oriented toward the participant. To facilitate the grasping, the key was enclosed in a metal ring. One first object – the shoebrush - was presented as an example and not scored. If the participant was unable to use it or made a mistake, the experimenter showed the correct gesture. Verbal instructions were the following: "I will place an object in front of you. Could you show me how to use this object? Please, use one hand only". Two separate scores were calculated for Grasp and Use. One point was given for a correct performance, while 0 points were given for an incorrect performance, with a maximum score of 23 points for both subscales. Grasp was defined as the first movement that was performed by the patient to pick up the object. Any further attempt to adjust the grip position in order to make a use possible (e.g. rotating the hammer in the hand until the metal top is perpendicular to the table) was considered as already part of Use scoring. Thus, a patient could grasp the object correctly but be unable to use it, or, conversely, grasp the object in a wrong way but then adjust the position and correctly use it. For example, if the pencil was grasped correctly but no writing movement was done, 1 point for Grasp, but 0 points for Use were assigned. Conversely, if a patient grasped the light bulb from the screw, then rotated the light bulb in the hand and made the correct movement, 0 points for Grasp and 1 point for Use were assigned. Four objects included in the final version (i.e. the fork, the ladle, the cake spatula and the shovel) could require more than one movement: a first movement to pick up something and a second movement to carry it toward the mouth (e.g. the fork) or toward another object (e.g. a plate for the ladle and the cake spatula, a vase for the shovel). Since German healthy participants often made only one of the two required movements, 1 point was assigned even if only one of the two movements was performed.

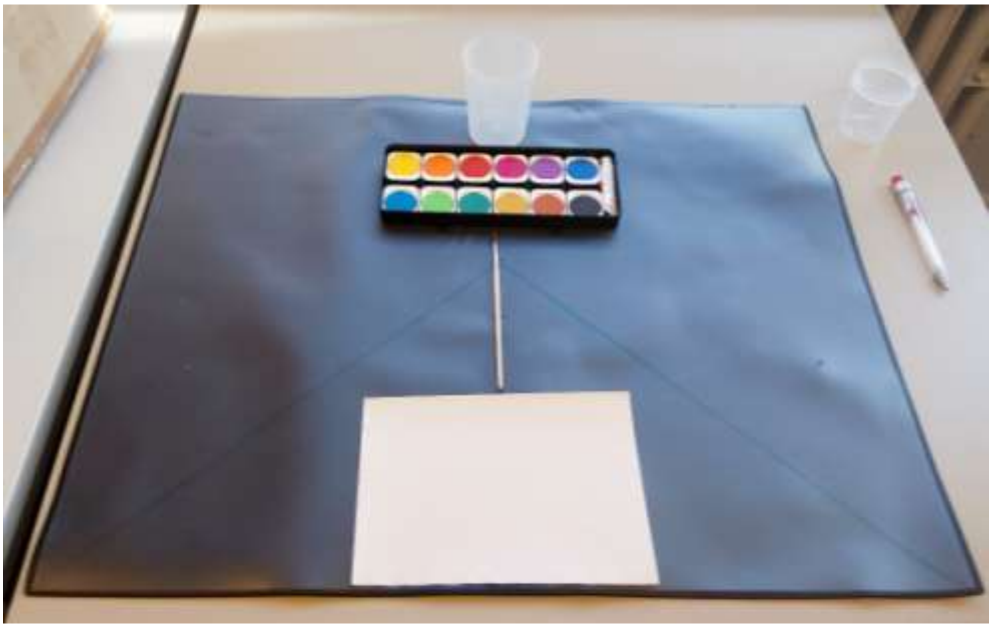
4.2.3.2 Multiple Object Use task (MOU)

This task was developed to test participants' ability to perform actions of increasing complexity with more than one object. Again, all actions could be performed with one hand only. The task included eight actions of increasing complexity on the basis of the correct steps that were required. The easiest action involved only two objects (i.e. a piggybank and a coin) and two steps (i.e. to pick up the coin, to insert the coin in the piggybank) while the most difficult action involved 4 objects (i.e. a stamp holder with a rubber stamp, an ink pad and a sheet of paper) and 5 steps (i.e. to open the inkpad, to pick up the stamp, to put the stamp on the inkpad to take some color, to put the stamp on the paper sheet, to place the stamp back on the holder). One point was assigned for each step that was successfully performed. Possible errors were classified as following: wrong selection (the subject selects first another object instead of the right one), wrong grasping (the object is grasped in a wrong, unusual way), misuse (the movement with the object is carried out in an awkward and ineffective way), sequence errors (the subject performs a correct action with the appropriate object, but it is carried out without having done an action that has to come before to reach the action goal). If the participant made a wrong object selection or a sequence error, but then made spontaneous auto-correction, all points were scored except of the step that was autocorrected. For example, the participant took the stamp from the holder before opening the inkpad, but then put the stamp on the table, opened the inkpad and performed the action correctly. In this case, only the first step (i.e. to open the inkpad) was scored 0, while the further 4 steps were scored 1 point each. Conversely, the participant could try to light the candle before putting it on the candlestick. In this case, the whole sequence was wrong and then 0 points were assigned. The maximum score for the MOU task was 28 points. A description of the 8 actions is given in Table 2. A plastic panel with signed positions was used to place the objects in the same way across testing sessions. One practice item, not scored (Figure 1), was given in the beginning, allowing the participant to comprehend the task. If the patient failed in this item, the experimenter showed the correct action. Before each trial, the experimenter reminded the subject to use one hand only and to wait until the experimenter had placed all the objects and gave the “go” signal before starting to perform the action. Verbal instructions were the following: “I will place here, in front of you, some objects. Could you show me how to use these objects in a proper manner? Please, do it with one hand only and wait until I have placed all the objects before starting”. If the participant looked at the objects hesitatingly, giving signs of not knowing what to do (for example he/she picked up one of them, turned it over, put it down, then tried with another object), the tester could help him/her by giving a further information on the purpose of the action (e.g. could you show me how to stamp a paper sheet?). If this further information was given, then half of the total points for that action was assigned (e.g. 2.5 points out of 5 total points for the stamp action).

Table 2. List of the 8 actions of the MOU task, divided in steps, and the relative scores. The objects that were presented in the actions are the following: 1. a piggybank and a coin; 2. a drinking package and its straw; 3. a glass bottle with its cap and a bottle opener; 4. a hole puncher and a paper sheet; 5. a letter in its envelope with a written address, a stamp and a stamp sponge; 6. a cash box and its key; 7. a candle, a candlestick and a lighter, 8. a rubber stamp in a holder, an ink pad and a sheet of paper.

ACTION	STEPS	SCORE
1. Piggybank (max 2 points)	- Pick up the coin - Insert it in the piggybank	1 1
2. Drinking package (max 3 points)	- Pick up the straw - Poke it in the drinking package - Carry it toward the mouth	1 1 1
3. Bottle cap (max 3 points)	- Pick up the bottle opener - Put the opener on the cap - Remove the bottle cap	1 1 1
4. Hole puncher (max 3 points)	- Take the sheet - Place the sheet into the punch - Punch a hole	1 1 1
5. Letter (max 3 points)	- Pick up the stamp - Wet the stamp on the sponge - Place the stamp on the letter	1 1 1
6. Cash box (max 4 points)	- Pick up the key - Insert the key in the lock - Turn the key - Open the box	1 1 1 1
7. Candle (max 5 points)	- Pick up the candle - Put the candle on the candlestick - Pick up the lighter - Move the lighter toward the candle - Light the candle	1 1 1 1 1
8. Stamp (max 5 points)	- Open the inkpad - Take the stamp from the holder - Press the stamp on the ink pad - Press the stamp on the paper - Place the stamp back on the holder	1 1 1 1 1
	Total score	...../28

Figure 1. An example of one item (practice item) of the MOU task. The participant is required to pick up the paintbrush, take some water from the glass, take some color from the palette and then paint on the sheet of paper.

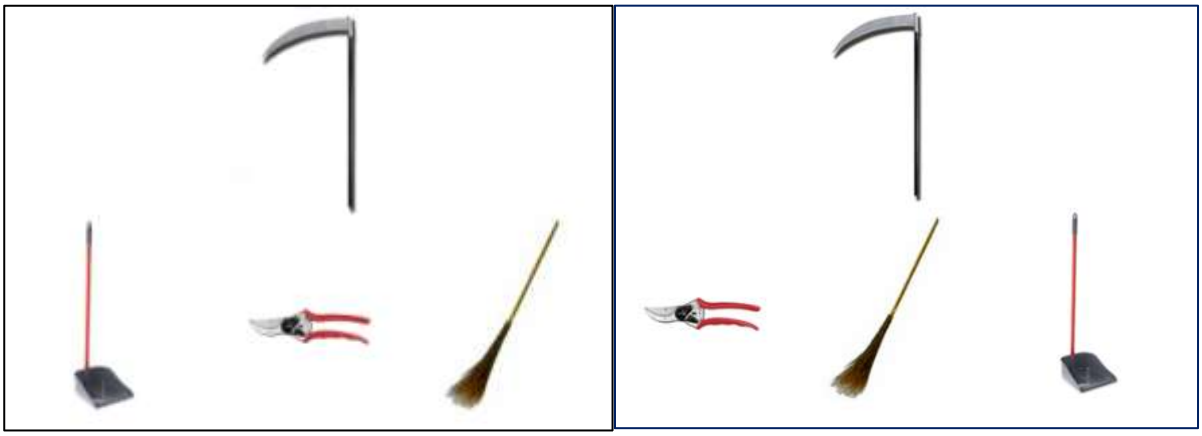


4.2.3.3 Manipulation/Function task

In this task, participants viewed a slide on a screen with an object picture on the top (probe) and three object pictures below it. One of the three objects corresponded to the target for Manipulation, one to the target for Function and the other one was a visual foil. Each slide was presented twice, one in the Manipulation and one in the Function block. The only variation between the two blocks was the item position in the slide. This choice allowed having the same stimuli in both conditions, thus controlling for item variability in the two blocks. However, repetition of the same stimuli may cause either a better performance on the second block, than on the first block (because the participant may exclude the item that he/she had chosen before), or on the first, than on the second block (because the participant may choose the same item that was previously selected without evaluating all the alternatives). To take into account this potential presentation effect, the two blocks were presented in a randomized order across participants and participants were encouraged, for each trial, to look carefully to all alternatives. Furthermore, before each trial the experimenter repeated the verbal instructions and the required type of association (Manipulation or Function).

Probe-target couples in the Manipulation condition were objects that could be afforded and used with the same gesture (e.g. scythe - broom). Probe-target couples in the Function condition were objects that could be used for the same purpose, such as to cut (e.g. scythe – garden shears). The foil shared the visual shape with the probe and could be partially afforded in the same way, but both the typical gesture and the function differed from the probe (e.g. scythe - dustpan). An example of two complementary slides for the Manipulation and Function conditions is given in Figure 2. Four example slides, not scored, for each condition, were presented before each block. If the participant made a wrong choice, the experimenter gave the correct answer and also explained why the other two options were wrong. Verbal instructions for the Manipulation condition were the following: "*You will see on the screen a slide with an object on the top and three other objects below it. You have to choose which of the three objects displayed below can be manipulated in the same way as the object on the top. There is only one right answer. Before starting, let's do some examples together*". Instructions for the Function block were the following: "*You will see on the screen a slide with an object on the top, and three other objects below it. You have to choose which of the three objects displayed below shares the same function as the object on the top. There is only one right answer. Before starting, let's do some examples together*". A first pool of 46 trials were tested on the German healthy group. After data collection, 11 trials for both Function and Manipulation blocks were excluded from the sample, because about 28 percent of participants made an error on them. The final version of the task included 35 trials for each block. One point was given for a correct answer, 0 points were given for a wrong answer. To avoid that co-occurrence of agnosia or other visual deficits may negatively influence performance on the Manipulation/Function task, a Recognition task, including all probe pictures used in the Manipulation/Function task, was applied before. In this task participants viewed an object picture and two words, referring to objects. One word was corresponded to the object picture, the other one was the word corresponding to another object picture of the task. If the participant had a severe performance on this task, the Manipulation/Function task was not administered. Furthermore, since the recognition task included all the probe stimuli of the Manipulation/Function task, if the participant made an error in the Recognition task, the corresponding trials in the Manipulation and Function conditions were not scored. In this case, the scores obtained in the two blocks were based on a lower number of total trials, and were proportionally corrected to be comparable to participants who had a flawless performance in the Recognition task. For example, if a patient made two errors in the Recognition task, the number of correct response in each block was calculated for 33 out of 35 items and the total score was obtained by the multiplication of the number of correct response * 35/33.

Figure 2. An example of a slide of the Manipulation block (on the left) and the corresponding slide in the Function block (on the right). The only variation between the two slides is items position. The scythe is the probe, the broom is the target in the Manipulation condition, the garden shears are the target in the Function condition, and the dustpan is the foil.



4.2.3.4 Semantic Association Task (SAT)

In this task participants were asked to associate the object picture that is located on the top of a card (probe picture) to one of two object pictures that are located below it. The task allows the calculation of 4 different scores, corresponding to distinct types of semantic association - *Categorical associations (CA;* the two items belonged to the same category, e.g. giraffe and zebra); *Encyclopedic associations (EA,* the two items were learnt to be related from school, e.g. cow and cheese); *Functional associations (FA,* the two items could be used together for a common purpose, e.g. screw and screwdriver); *Visual-encyclopedic associations (VEA*, the two items were associated mostly because they were seen together, in spatial proximity ,e.g. clown and circus tent). Four practice items (not scored) were presented before the task. Verbal instructions were the following: “Could you please indicate which of the two below pictures is related most, in your opinion, with the picture on the top?”. One point was given for each correct answer. The maximum score for each semantic association was 19, and 76 was the total maximum score. Cut-off scores for the total SAT score and for each type of semantic association were available from a previous study (see Chapter 2, paragraph 2.2.3). An example of cards used in this task is given in Chapter 2, paragraph 2.2.3, Figure 1.

4.2.4 Procedure

The same procedure was adopted for patients and for Italian and German healthy participants. First, all participants were asked to complete the Oldfield Inventory to establish the handedness Laterality Quotient (LQ), and healthy participants were tested with the MMSE. Then, the SAT, the two Object Use tasks and the Manipulation/Function task were applied on German healthy participants in a randomized order in a unique session. Italian healthy participants were also tested with the German version of the two apraxia tests (GIT and CAS), because normative data for Italians are not available. Since patients with dementia could have Ideo-Motor apraxia for their dominant right hand, before starting the testing session each patient was asked to choose which hand he/she wanted to use in the tasks. All patients included in the study decided to use their right hand.

4.2.5 Statistical Analysis

Since the sample size is not large enough to have a good power, the analysis reported for the present study is still explorative and have to be interpreted carefully. In fact, a-priori power analysis showed that a sample size of 46 participants is required to conduct bivariate correlations (*two tailed, correlation for H1 = .40, power = .8; α = .05*) and a simple regression (*two tailed, effect size = .20,* *power = .8; α = .05*). In patients, MOU score had a relatively normal distribution (*Asymmetry: -0.60 ± 0.50; Kurtosis: 0.19 ± 0.97, Shapiro-Wilk test (21) = .95, p = .320*), while SOU violated the test for normal distribution (SOU_Use: *Shapiro-Wilk test (21) = .89, p = .023;* SOU_Grasp: *Shapiro-Wilk test (21) = .53, p = .000*), although Kurtosis (SOU_Use: *-1.2* ± *.97;* SOU_Grasp: *-0.28* ± *.97*) and Asymmetry (SOU_Use: *-0.27* ± *0.50;* SOU_Grasp: *-1.33* ± *0.50*) values were relatively acceptable. Italian patients and healthy participants were compared on demographic variables and on all the tasks included with non-parametric Mann-Whitney test and chi-squared analysis (for gender distribution only). Spearman correlation analyses were conducted to explore common variations between the two dependent variables (performance on SOU and MOU) and the other tasks. Spearman correlations were preferred to Pearson's because they are more reliable for small samples. The relationship among the two Object Use tasks, apraxia tasks, general semantics and object semantics tasks was further explored with multiple regressions. Furthermore, to test whether manipulation or function knowledge could predict the outcome (deficit vs. normal performance) of the object use performance, the MOU and the SOU_Use continuous variables were dichotomized on the basis of cut-off scores (calculated on healthy participants'performance) and logistic regressions were conducted. Finally, to explore potential differences between Grasp and Use subtests of SOU in patients, an item-by-item analysis with contingency tables and Chi Squared tests was conducted for each object of the SOU task.

4.3 RESULTS

4.3.1 Task Comparisons in the Patient group

4.3.1.1 Patients' performance and Correlation Analysis

Patient's scores on all the experimental tasks and the two apraxia tests (GIT and CAS) are reported in Tables 3 and 4. Cut-off scores for the experimental tasks were calculated on the basis of Italian healthy participants by subtracting 2 Standard Deviations from the mean scores. Since all Italian healthy participants had comparable performances to German healthy controls on the GIT and on the CAS, cut off scores of the original tests were maintained. Two separated Spearman correlation analyses were conducted for Italian patients and healthy participants. As regards demographic variables, Age was not correlated with any measure in both groups. Educational level significantly correlated with the total SAT score ($\rho = .589, p = .005$), and with its corresponding CA, EA and VEA subtests (*CA:* $\rho = .482, p = .027$; *EA:* $\rho = .477, p = .029$; *VEA:* $\rho = .540, p = .011$), but not with FA subtest ($\rho = .283, p = .214$), in the patient group, while in the control group the educational level had a significant negative correlation with VEA subset only ($\rho = -4.95, p = .027$). No other significant correlation was detected in the control group. Patients' performance on MOU significantly correlated with performance on SOU Use ($\rho = .594, p = .005$). Performance on MOU significantly correlated with POU_L subtest of CAS ($\rho = .593, p = .005$), total CAS score ($\rho = .550, p = .010$), Manipulation ($\rho = .453, p = .039$), and Function ($\rho = .536, p = .012$). Performance on SOU Use significantly correlated with FA subset of SAT ($\rho = .514, p = .017$), POU_L subtest of CAS ($\rho = .485, p = .026$), CAS total score ($\rho = .459, p = .036$), and Function ($\rho = .610, p = .003$). No significant correlation was found for SOU Grasp. Furthermore, SAT scores significantly correlated with Function (*SAT tot:* $\rho = .761, p = .000$, *CA:* $\rho = .437, p = .048$; *EA:* $\rho = .715, p = .000$; *FA:* $\rho = .563, p = .008$; *VEA:* $\rho = .720, p = .000$), Manipulation (*SAT tot:* $\rho = .566, p = .007$, *CA:* $\rho = .435, p = .048$; *EA:* $\rho = .448, p = .042$; *VEA:* $\rho = .615, p = .003$), POU_L subtest of CAS (*SAT tot:* $\rho = .554, p = .009$, *EA:* $\rho = .539, p = .012$; *FA:* $\rho = .465, p = .034$; *VEA:* $\rho = .521, p = .015$) and total CAS score (*SAT tot:* $\rho = .560, p = .008$, *EA:* $\rho = .574, p = .006$; *FA:* $\rho = .502, p = .020$; *VEA:* $\rho = .514, p = .017$). Accordingly, significant correlations were detected also between CAS scores and both Function (*POU_L:* $\rho = .578, p = .006$; *CAS tot:* $\rho = .552, p = .009$) and Manipulation (*POU_L:* $\rho = .479, p = .028$; *IML:* $\rho = .525, p = .015$; *CAS tot:* $\rho = .637, p = .002$). Interestingly, GIT scores showed no significant correlation but between FA subset of SAT and the GIT hand subscale ($\rho = .474, p = .030$).

Table 3. Patients' performance on the two Object Use tasks, the Manipulation/Function task and the Semantic Association Task (SAT). Legend: MOU = Multiple Object Use task, SOU_Use = Use subtest of the Single Object Use task, SOU_Grasp = Grasp subtest of the Single Object Use task, Man = Manipulation block, Fun = Function block, SAT Tot = Total SAT score, SAT CA = Categorical Association subset of SAT, SAT EA = Encyclopedic Association subset of SAT, SAT FA = Functional Association subset of SAT, SAT VEA = Visual-Encyclopedic Association subset of SAT. In bold: scores below the cut-off. Underlined scores: scores at a borderline level. Cut-off scores calculated as 2 standard deviations below healthy participants' mean: MOU ≥ 25, SOU_Use ≥ 22, SOU_Grasp ≥ 22, Man ≥ 20, Fun ≥ 23. Cut off scores available from a previous study: SAT Tot ≥ 50, SAT CA ≥ 11, SAT EA ≥ 13, SAT FA ≥ 14, SAT VEA ≥ 13.

Case	**MOU**	**SOU_Use**	**SOU_Grasp**	**Man**	**Fun**	**SAT Tot**	**SAT CA**	**SAT EA**	**SAT FA**	**SAT VEA**
LB	28.0	23	23	25.0	29.0	70	17	18	17	18
PV	**24.0**	22	23	**10.6**	24.1	59	14	**12**	17	16
FP	**24.5**	**19**	23	**12.0**	**16.3**	54	16	13	**12**	13
GP	25.0	**21**	22	23.0	26.0	69	14	19	17	19
GE	26.0	22	23	21.0	24.0	69	16	16	19	18
GB	22.0	**21**	23	21.7	**15.0**	57	15	**12**	14	16
AC	27.0	22	23	**15.0**	**18.5**	62	17	15	15	15
CC	25.0	22	23	**16.0**	27.0	73	17	19	18	19
MP	25.5	23	22	22.0	28.0	72	18	17	19	18
MG	23.0	**20**	23	**19.0**	**18.0**	66	18	15	16	17
FPA	26.0	**21**	23	22.0	**22.0**	69	17	16	18	18
GR	26.0	**20**	23	30.0	27.0	71	18	17	18	18
TC	20.0	**19**	22	**13.0**	**22.0**	62	15	16	15	16
AF	26.0	**20**	22	**17.5**	**19.1**	66	16	16	17	17
ACA	23.0	**20**	22	**14.8**	**19.1**	61	14	13	18	16
MM	23.0	**20**	23	20.0	26.0	73	18	18	18	19
RB	26.0	22	23	**18.6**	24.8	61	15	17	15	14
IS	24.0	23	23	**18.0**	24.0	69	16	17	19	17
NM	28.0	23	23	21.0	30.0	74	18	19	18	19
GPA	27.0	22	23	26.0	26.0	72	17	17	19	19
ACI	28.0	23	23	21.0	27.0	66	17	13	19	19

Table 4. Patients' performance on the Cologne Apraxia Screening (CAS) and on the Goldenberg Imitation Test (GIT). Legend: CAS tot = total score on CAS, POU_L= pantomime of object use with the upper limb of CAS, IML= imitation of gestures with the limb of CAS, POU_O= pantomime of oral object use of CAS, IMO = imitation of oral gestures of CAS, GIT_H = Hand subscale of the Goldenberg Imitation test, GIT_F = Finger subtest of the Goldenberg Imitation Test. In bold: scores below the cut-off. Underlined scores: scores at a borderline level. Cut-off scores as in the original tasks: CAS tot ≥ 77, GIT_H ≥ 18, GIT_F ≥ 17.

Case	CAS Tot	POU_L	IML	POU_O	IMO	GIT_H	GIT_F
LB	77	20	20	19	18	**17**	18
PV	**60**	14	14	14	18	18	20
FP	**72**	20	16	18	18	**17**	**16**
GP	80	20	20	20	20	19	19
GE	78	20	20	18	20	20	19
GB	**69**	14	20	15	20	18	19
AC	78	18	20	20	20	20	19
CC	78	20	20	18	20	20	20
MP	79	20	20	19	20	19	20
MG	**72**	18	20	14	20	20	**14**
FPA	**76**	18	18	20	20	19	20
GR	80	20	20	20	20	20	20
TC	**62**	16	8	18	20	**14**	**14**
AF	**70**	18	16	20	16	20	20
ACA	**68**	12	20	20	16	20	**16**
MM	**73**	16	20	19	18	20	17
RB	78	18	20	20	20	20	**16**
IS	78	20	18	20	20	20	19
NM	77	20	18	19	20	20	19
GPA	80	20	20	20	20	20	20
ACI	78	20	20	20	18	20	17

4.3.1.2 Influence of Pantomime and Apraxia on the two Object Use tasks

Two separated stepwise multiple regressions with backward method were conducted to investigate whether POU_L score and the total score of CAS significantly predicted performance on MOU and on SOU_Use scores. Results showed that CAS total score significantly predicted performance on both Object Use tasks (MOU: B *coefficient* $= .249$, β *coefficient* $= .688$, $F(1, 20) = 17.04$, $p = .001$, $R^2 = .473$; SOU_Use: B *coefficient* $= .116$, β *coefficient* $= .496$, $F(1, 20) = 6.22$, $p = .022$, $R^2 = .246$). Furthermore, the two dependent variables were dichotomized (0 = deficit; 1 = normal performance) on the basis of the two cut-off scores computed on Italian healthy participants' performance and two logistic regressions were conducted with total CAS scores as independent variable. The binomial test showed that 1 (normal performance) and 0 (deficit) outcomes had equal probability in both MOU (*Frequency of 1 = 13/21, Frequency of 0 = 8/21, Observed Proportion = .62, p = .38*) and SOU tasks (*Frequency of 1 = 11/21, Frequency of 0 = 10/21, Observed Proportion = .50, p = 1.0*). Results of the logistic regressions showed that higher CAS scores significantly increased the probability of a spared performance (value = 1) on MOU (*B coefficient = .496, Exp (B) coefficient = 1.642, p = .014;* χ^2 *(1) = 13.87, p = .000*) but not on SOU_Use task (*B coefficient = .156, Exp (B) coefficient = 1.169, p = .116;* χ^2 *(1) = 3.19, p = .074*).

4.3.1.3 Influence of Action semantics and Object semantics on the two Object Use tasks

Two separated stepwise multiple regressions with backward method were conducted to investigate whether performance on Manipulation, Function, SAT total score and SAT FA subset score significantly predicted performance on MOU and on SOU_Use scores. Results showed that Function was the only significant predictor for both Object Use tasks (MOU: *B coefficient = .250, β coefficient = .515, F (1, 20) = 6.86, p = .017,* R^2 *= .265;* SOU_Use: *B coefficient =.188, β coefficient = .601, F (1, 20) = 13.24, p = .004,* R^2 *= .361*). These results were only partially confirmed by the two logistic regressions with dichotomized MOU and SOU_Use variables. In fact, for the SOU_Use task, logistic regression kept both Manipulation and Function in the final model, but only Function significantly predicted the probability of spared performance on SOU_Use (*B coefficient = .530, Exp (B) coefficient = 1.699, p = .020;* χ^2 *(2) = 9.80, p = .007*). Conversely, logistic regression for MOU showed that higher Manipulation, but not Function, scores significantly increased the probability of a spared performance on MOU (*B coefficient = .342, Exp (B) coefficient = 1.407, p = .031;* χ^2 *(1) = 7.41, p = .006*).

4.3.1.4 Influence of Action semantics and Apraxia on the two Object Use tasks

Two final logistic regression were computed with Manipulation, Function and Total CAS score as independent variables and dichotomized SOU_Use and MOU scales as dependent variables. For MOU task, the analysis revealed that CAS score could be the unique significant predictor and results were the same as those reported in paragraph 4.3.1.2. For SOU_Use task, instead, the model was significant when all three variables were included ($\chi^2(3) = 16.56, p = .001$). Manipulation and Function were significant predictors (*Manipulation:* $p = .043$*; Function:* $p = .03$) and there was a trend also for total CAS score ($p = .05$). However, while higher values of Function and CAS significantly predicted the probability of a spared (value = 1) outcome on SOU, lower Manipulation scores significantly predicted the probability of a defective (value = 0) outcome on SOU (Table 5).

Table 5. Results of Logistic regression with dichotomized (0 = deficit, 1 = normal performance) SOU_Use as dependent variable and Manipulation, Function and CAS total score as independent variables. Legend: B= B coefficient, df = degrees of freedom, p = significance level, Exp (B) = Expected B coefficient.

	B	*df*	*p*	*Exp(B)*
MANIPULATION	-0.799	1	0.043	0.450
FUNCTION	0.842	1	0.030	2.322
total CAS score	0.471	1	0.050	1.602
Constant	-39.492	1	0.032	0.000

4.3.2 Group Comparisons

Italian patients and healthy participants did not differ on Age ($p = .89$) and on Gender distribution ($\chi^2(1) = .672, p = .412$), but significantly differed on Educational level ($p = .043$). Patients performed significantly worse than healthy participants on almost all the experimental tasks, but had comparable scores to that obtained by the control group in the hand subscale of GIT and in the Grasp subtest of the SOU task (Figure 2 and Table 6).

Figure 2. Comparison between patients and healthy participants on mean raw values for all the tasks included in the study. To facilitate task comparisons, correct responses on Y axis are expressed as percentages. Legend: HC = Healthy Controls. * Statistically different at p < .05, ** statistically different at p < .01, *** statistically different at p < .001.

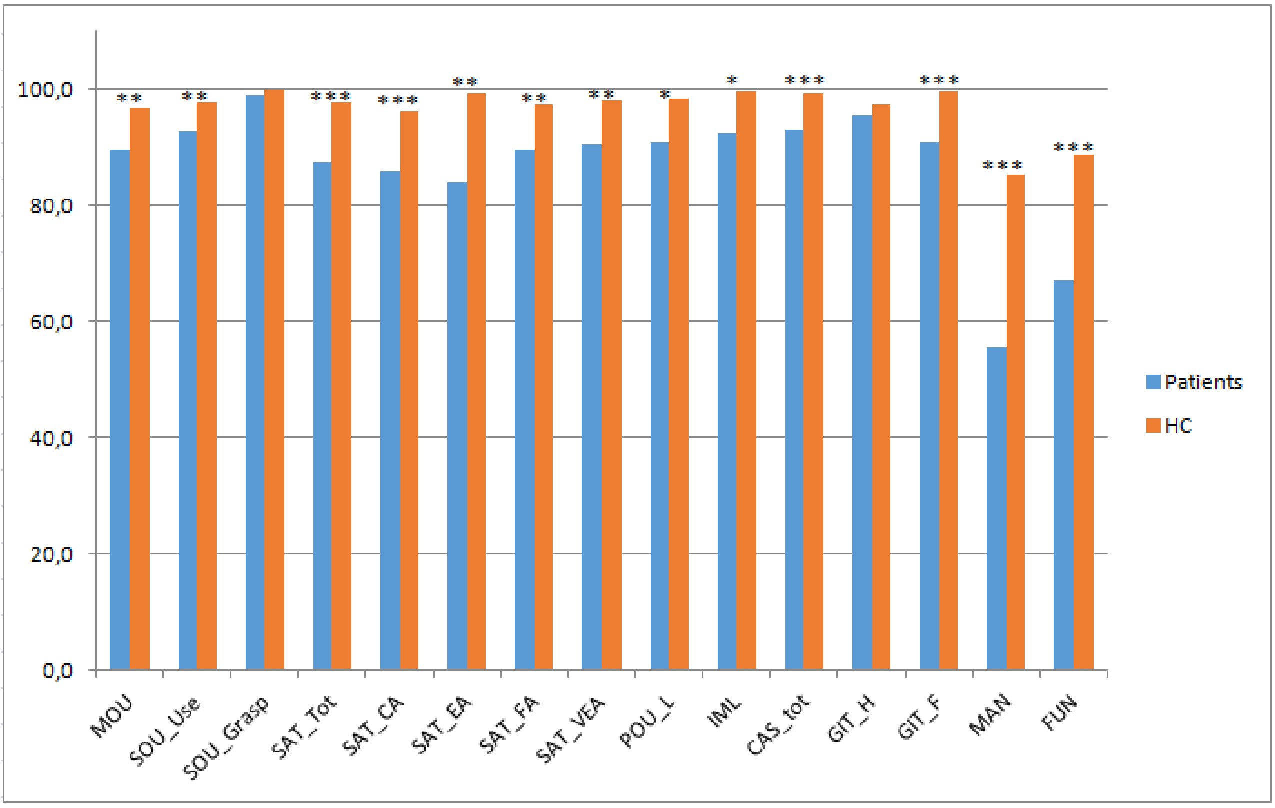


Table 6. Mean values and Standard Deviations for Patients (on the top) and Healthy Controls (on the bottom).

MOU	SOU Use	SOU Grasp	SAT Tot	SAT CA	SAT EA	SAT FA	SAT VEA	POU _L	IML	CAS Tot	GIT Hand	GIT Finger	MAN	FUN
25.1	21.3	22.8	66.4	16.3	16.0	17.0	17.2	18.2	18.5	74.4	19.1	18.2	19.4	23.5
2.1	1.4	0.4	5.8	1.4	2.2	1.9	1.7	2.4	3.0	5.8	1.5	2.0	4.8	4.3
27.2	22.5	23.0	74.3	18.3	18.9	18.5	18.7	19.7	19.9	79.4	19.5	20.0	29.9	31.1
1.0	0.5	0.2	1.5	1.0	0.4	0.6	0.6	0.7	0.4	1.0	0.8	0.2	4.8	3.6

4.3.3 Grasp versus Use

Performance on Grasp and Use subtests of the SOU was compared within patients with and item by item analysis. Only objects in which at least one error occurred, on either Grasp or Use, were included in the analysis. Fourteen of the 23 objects were included (eraser, hammer, jug, key, light bulb, cake spatula, saw, table tennis racket, roll paintbrush, hairbrush, ice scraper, shovel, remote control). Contingency tables and Chi squared tests showed that patients' performance on Grasp and on Use dissociated for the table tennis racket ($\chi^2 (1) = 4.42, p = .035$) and the ice scraper ($\chi^2 (1) = 9.88, p = .002$), but there was also a trend for the cake spatula ($\chi^2 (1) = 3.23, p = .072$) and the hairbrush ($\chi^2 (1) = 3.23, p = .072$). For these two latter items, 3 patients had a normal performance (value = 1) on Grasp, but made an error on Use (value = 0) whereas the remaining 18 patients had normal scores on both measures. For the table tennis racket, 14 patients performed correctly on both Grasp and Use, whereas 4 patients obtained 1 point on Grasp but 0 points on Use. When considering the ice scraper, results were similar, and 8 patients grasped the object correctly but then had a deficit of Use.

4.4 DISCUSSION

Current literature on tool use abilities (see also paragraph 1.3.4) is divided between theories that give an important role to some kind of semantic object knowledge (e.g. manipulation or function knowledge) to perform tasks that involve the actual use of objects (manipulation-based approach, Buxbaum, 2017) and theories that deny such role for semantic knowledge but give importance to other cognitive processing, such as technical reasoning (technical reasoning hypothesis, Osiurak & Badets, 2016; Baumard et al., 2016). The present study was part of a larger project in collaboration with the University Clinic of Cologne, involving a sample of German healthy participant and a sample of German stroke patients. Here, only data on Italian healthy participants and Italian patients with Alzheimer's disease are presented. The aim of the study was to investigate whether data on neurodegenerative patients were in agreement, or, conversely, against the manipulation-based approach and/or the technical reasoning hypothesis predictions. A previous study (Baumard et al., 2016) conducted an investigation on different types of neurodegenerative disease to address the issue whether manipulation knowledge is necessarily involved in object use abilities. This study included two different tool use tasks (single tool use and tool-object recipient use), a mechanical problem solving task (which is assumed to require technical reasoning) and a functional/contextual association task between object pictures. Final results, and especially those obtained on AD patients, were only partially in agreement with both technical reasoning and manipulation-based hypotheses. However, this study did not include a task that could be a reliable measure of manipulation knowledge and thus it was not possible to evaluate whether impaired manipulation correlated with significant deficits on the two tool use tasks. In the current study, a manipulation/function association task was included, as well as a general semantic association task (SAT), an extensive battery for apraxia (CAS), a test for meaningless postures (GIT for hand and finger gestures), a single object use task (SOU) and a multiple object use task (MOU). The manipulation/function task and the two object use tests were specifically designed for the study (see paragraphs 4.2.3.1, 4.2.3.2, 4.2.3.3). In particular, the two objects use tasks were developed with the aim to include only actions that could be performed with one hand only. This point is really important when the tasks are applied on stroke patients, who often have hemiparesis and are not able to use one hand (which may also be the dominant hand). In addition, if the patient can execute all gestures with one hand only, the experimenter is facilitated in evaluating if the gesture is correct or wrong. Moreover, different from other studies that investigated tool use abilities in patients (Baumard et al., 2016; Martin et al., 2016; Buchmann & Randerath, 2017), in the multiple object use task it was decided to include actions requiring more than one movement and more than two objects, rather than evaluating only tool-recipient actions. This decision was made in order to evaluate complex actions that could be similar to those that are executed in everyday life. Furthermore, recent studies demonstrated that the way in which we grasp objects may dissociate from the way in which we use them (Binkofski & Buxbaum, 2013). Thus, in the SOU task two separate scores for Grasp and Use were included. Correlation analysis (see paragraph 4.3.1.1) revealed that patients' scores on MOU task significantly correlated with scores obtained in both the Manipulation and the Function blocks of the Manipulation/Function task, in the subtest of CAS requiring to pantomime the use of an object with the upper limb (POU_L), and in the total CAS battery. This result is in agreement with the manipulation-based approach, which claims that both manipulation and function are engaged when we need to use objects in a purposeful manner, and especially when we need to execute complex naturalistic actions. In fact, complex actions require an integration of information about the structural description of the objects and about the specific hand and arm postures to use them (i.e. affordance and Manipulation knowledge) with semantic knowledge on the specific functional properties of objects and the purpose of their use (van Elk et al., 2014). Patients' performance on SOU Grasp did not significantly correlate with any other task, whereas patients' performance on SOU Use significantly correlated with scores obtained in the Function Association subset of SAT, in the Function block of the Manipulation/Function task, in the POU_L and in the CAS total scale. Interestingly, no significant correlation was detected between performance on SOU Use and Manipulation knowledge. Although this result may appear in contrast with the manipulation-based approach, significant correlations with function knowledge in both SAT and Manipulation/knowledge tasks may suggest that a relative sparing of Function knowledge, processed in the ventral stream, could partially compensate for degraded Manipulation knowledge in the ventro-dorsal stream, in agreement with the manipulation-based approach predictions (Buxbaum, 2001). Finally, significant correlations were identified between CAS total score and CAS pantomime of object use with both Manipulation and Function scores. The gestures imitation subtest of CAS and the two meaningless gestures lists (GIT_H, GIT_F), instead, did not significantly correlate with either the object use tasks or the Manipulation/Function task. To further investigate the role of praxis measures and Manipulation and Function knowledge in object use, a series of multiple and logistic regressions was conducted. First, two separated multiple regression aimed at quantifying the effect of praxis on MOU and on SOU Use performance, introducing the CAS total score and the POU_L score as independent variables (see paragraph 4.3.1.2). The best model included only the total CAS score as potential predictor, with a significant effect on performance obtained in both object use tasks. To conduct logistic regressions, the two continuous dependent variables were split into two possible scores (1, 0) indicating a spared performance (value = 1) or a defective performance (value = 0), on the basis of cut-off scores that were calculated on healthy participants' performance. The logistic regressions confirmed that higher CAS total scores significantly predicted the probability to be spared (value = 1) in both the MOU and the SOU Use tasks. In a parallel way, two other multiple regressions (see paragraph 4.3.1.3) were conducted for SOU Use and MOU to investigate the role of Manipulation, Function, and two other object semantic measures (SAT total score and FA subset). Results showed that performance on the Function subtest of the Manipulation/Function task significantly predicted the performance on the two object use tasks, while all the other variables were excluded from the final significant model. However, results on the complementary logistic regressions partially differed from those of multiple linear regression. For the SOU task, both Manipulation and Function were kept in the model, but only Function had a significant effect in determining a higher probability of a spared outcome (value = 1). Conversely, for the MOU task, performance on Manipulation was the only independent variable that was kept in the final model and significantly predicted the probability of a spared outcome. Thus, two final logistic regressions with Manipulation, Function and total CAS score as independent variables were conducted (see paragraph 4.3.1.4). Interestingly, for the SOU Use task, the model included all three variables, which had different effects on the SOU outcome: while higher scores in Function and, to a lesser extent, in the total CAS battery, significantly predicted the probability of a positive outcome, lower performance on Manipulation significantly predicted the probability of a negative outcome (value = 0). Finally, results on the logistic regression for MOU revealed that only the total CAS score was included in the final model and significantly predicted a positive outcome. To sum up, results obtained in the present study are in agreement with the predictions made by the manipulation-based approach. In fact, the final logistic regression on SOU Use demonstrated that when Manipulation was impaired, patients had higher probabilities of impaired demonstration of the correct use of an object. Furthermore, spared performance on Function significantly predicted a positive outcome on SOU Use task. These results suggest that when manipulation is damaged, patients may benefit from access to function knowledge in understanding the purpose of use of the object that they were faced with. This semantic facilitation, combined with partially preserved praxis abilities, may allow patients to correctly manipulate the object. This hypothesis is in agreement with current literature on action semantics (van Elk et al., 2014), which states that knowledge about functional properties of tools may be used to select manipulation knowledge (i.e. how to grasp the tool). Furthermore, function knowledge may enable us to select, among infinite ways in which the hand can be brought to an object, which are the appropriate movements of the arm, the hand, and the body to perform whatever action with an object (inverse-kinematic problem; Rosenbaum et al., 1995). However, results of the present study have to be interpreted carefully, because statistical analyses were conducted under power, since the patient sample size was lower than what it would be expected from the a-priori power analysis. Furthermore, when looking at single cases' performance, it seems that the manipulation-based approach alone do not fully explain all possible patterns of performance. In some cases (CC, RB and IS) a lack of deficit on either SOU or MOU, despite an impairment of manipulation knowledge, may be explained by a compensation of intact function knowledge. However, in another case (AC), although Manipulation and Function knowledge were damaged, the patient performed within normal ranges on both object use tasks. These data are strongly against the manipulation-based hypothesis, and may suggest that when both manipulation knowledge and function knowledge were defective, patients could use other cognitive processes, such as spared technical reasoning, to compensate for relevant semantic object knowledge deficits. This possibility is not investigated by the present study, but could be an important issue for future research. Another important result is the impact of apraxia on tool use deficits. In particular, the score of the apraxia battery significantly predicted patients' performance on both object use tasks. This is evident in cases MM, GB, and FPA who had an affected performance on one of the two tool use tasks, relative spare of manipulation, but impaired scores on the CAS. However, two other cases (GP and GR) had a defective performance on at least one of the two tool use deficits in absence of abnormal performance on any other task. A high heterogeneity between AD patients' performance on object use, praxis and semantic tasks was found also in the study of Baumard and colleagues (2016). As it was hypothesized, object use disorders in Alzheimer patients may result from cognitive impairments that were not taken into account (e.g. general problem solving skills). Finally, results on Grasp and Use subtests of the SOU task revealed that these two components are dissociable. In fact, patients' performance on SOU Grasp and SOU Use was not correlated and sometimes (especially when using the ice scraper and the table tennis racket) patients could grasp the object correctly but then be unable to use it. This latter result is in agreement with the manipulation-based approach prediction, but in strong contrast with the technical reasoning approach. In fact, the technical reasoning hypothesis posits that both grasp and use of objects rely upon intact mechanical knowledge and technical reasoning. Thus, when mechanical knowledge and/or technical reasoning are disrupted, both the grasp and the use of objects should be impaired. Interestingly, no dissociation in terms of wrong grasping and spared use was detected. A recent study (Jax & Buxbaum, 2010) showed that there are two possible types of grasp - a grasp that relies upon functional properties of objects (i.e. grasp-to-use) and a grasp that relies upon the structural aspects of objects, which is employed, for example, when we just want to pick up an object to transport it. Thus, there is the possibility that our SOU task measures only the grasp-to-use component, not allowing us to find a correct use without a correct grasp. An enlargement of the patient sample may provide new information on this issue. In conclusion, results on the patient group suggest that manipulation knowledge is highly correlated with performance on object use task and, thus, has great relevance when we need to perform either actions with single objects or complex actions with more than one object. Furthermore, spared function knowledge may compensate for manipulation loss and allow patients to use objects in an efficient way. Apraxia for meaningless actions seems not to have a crucial role in tool use abilities, whereas defective performance obtained in a more extensive apraxia battery (e.g. including pantomime of object use) can account for tool use deficits, even in absence of manipulation or function knowledge loss. Moreover, the study demonstrates that grasp and use abilities, which are thought to be supported by distinct neural pathways (i.e. the dorso-dorsal and the ventro-dorsal stream, respectively; Binkofski & Buxbaum, 2013), may be differently performed, even for the same object. Overall, results obtained by this third experiment are in agreement with the manipulation-based approach and suggest that multiple cognitive pathways - i.e. the ventral stream, the ventro-dorsal stream, and the dorso-dorsal stream, subserving semantic object knowledge, manipulation knowledge and motor control, respectively - dynamically interact when we need to use objects in everyday life. However, some single cases suggested also that another possible mechanism (e.g. technical reasoning) may intervene in enabling correct object use even when these processes are partially damaged. Future research should focus on different patient populations (e.g. stroke patients) and may explore the relationship between technical reasoning and manipulation knowledge.

GENERAL DISCUSSION

Upper limb apraxia is a cognitive disorder related to motor control and skilled action execution, which cannot be explained by primary motor or sensory deficits, general cognitive decline or language comprehension difficulties. Core features of apraxia include the inability to imitate intransitive (meaningful or meaningless) and transitive (pantomime or tool-related) gestures, difficulties in pantomiming the use of an object, and object use deficits. Traditionally, the form of apraxia which causes inability to imitate gestures is called Ideo-Motor apraxia, whereas a predominant deficit in object use is called Ideational apraxia (Liepmann, 1908; De Renzi et al., 1968; De Renzi & Lucchelli, 1988). These two forms often present together after an infarction of the left hemisphere, and especially when lesions encompass the left inferior parietal lobe (see paragraph 1.1). In addition, patients with left hemisphere lesions often suffer from both limb apraxia and aphasia. This association may be explained in terms of anatomical proximity of neural pathways underlying language and praxis (Papagno et al., 1993). However, a recent study demonstrated that aphasic and apraxic symptoms, although dissociable, share common substrates, but regions of overlapping vary on the basis of the specific sub-components, of the disorders that are being compared (Goldenberg & Randerath, 2015). Some authors (Xu et al., 2009; Mengotti et al., 2013) have proposed that language and praxis systems involve overlapping neural pathways, particularly in the case of meaningful action imitation (see paragraphs 1.2.2 and 1.2.3). According to a prominent neurocognitive model (Rothi et al., 1991; Cubelli et al., 2000), different types of gesture are processed by two distinct pathways – a visuo-motor and a semantic route (see paragraph 1.1.4). The visuo-motor route allows the subject to observe the gesture that is executed by another person and translate the seen gesture into the corresponding motor program. This route is activated especially when we are asked to imitate unfamiliar gestures, but may be used to imitate all types of gesture. Conversely, the semantic route is used to imitate familiar, meaningful gestures by accessing their meaning in the gestural memory. Patients' performance on various tasks (e.g. imitation vs. recognition of gestures) and on different stimuli presentation (e.g. on verbal or on visual presentation) may be disproportionately affected on the basis of the level at which the semantic or the visuo-motor pathway is damaged. For example, a deficit in imitating familiar gestures but spared ability to recognize them would indicate damage at the input gesture lexicon level. Conversely, gesture recognition deficit would indicate damage to the semantic gestural memory. This model is complementary to the dual-routes model for reading aloud (Coltheart et al., 1993), which states that a lexical route is engaged to read familiar words, whereas a non-lexical route is used to process non-words or unknown words.

The first study of the present dissertation (chapter 2) was conducted to explore the relationship between gestural semantics (as measured by performance on meaningful gestures imitation), semantic processing, and linguistic abilities. The dual-routes model would predict a strong correlation between the imitation of meaningful gestures and the performance obtained in semantic or linguistic tasks. Meaningless gestures, instead, were expected to dissociate from semantic or linguistic performance. Furthermore, according to the model, the two routes could be selectively impaired, thus leading to double dissociations between meaningful and meaningless gestures observable in single-case analysis. However, a homogeneous performance on the two types of gesture may indicate that the visuo-motor route has also been involved in imitating meaningful gestures and can compensate for the semantic route deficit. Furthermore, the dual routes model predicts that meaningful transitive and intransitive gestures are represented in two different action input lexicons and thus are supported by distinct neural pathways (Cubelli et al., 2000; Dressing et al., 2016). The present study investigated patients' behaviour on three types of gestures - meaningless (unfamiliar) gestures, meaningful intransitive (symbolic) gestures, and meaningful transitive (pantomime of object use) gestures. Aphasia was evaluated through a validated battery of tests (Aachen Aphasia Test). Additional tasks - verb naming, verb comprehension, and semantic association - were included in the patients' evaluation (see paragraph 2.2.3). Results of group comparisons showed that healthy participants had a meaningful superiority effect, in that they obtained higher scores on meaningful gestures, than on meaningless, whereas patients showed an equally defective performance on both types of gesture (see paragraph 2.3.2.1). At the single-case level, many patients had selective or predominant damage to meaningful gestures, satisfying criteria for dissociation favouring meaningless over meaningful gestures (see paragraph 2.3.2.2). No patient exhibited a dissociation in the opposite direction. As expected, difficulties in execution of meaningful transitive gestures (pantomime of object use) double dissociated from damage to imitation of meaningful intransitive gestures. Thus, dissociated patterns demonstrate that different praxis abilities (as represented by performance on different types of gesture) are supported by distinct cognitive pathways, which can be selectively impaired. Furthermore, performance on imitation of meaningful, but not on meaningless, intransitive gestures significantly correlated with performance on the functional association subset of the Semantic Association Task (see paragraph 2.3.4). The functional association subset required access to action knowledge to decide which two objects could be used together to successfully complete an action (e.g. deciding that a toothbrush should be used with toothpaste). This evidence indicates that patients had a predominant deficit of the semantic route, due to impaired access of the semantic meaning in gestural memory, and that this deficit was also evident when they had to associate objects that could be used together in a purposeful action. In conclusion, results suggest that semantic action knowledge may be engaged in both semantic association tasks and praxis tasks that require access to symbolic meaning.

The second study in the present dissertation (chapter 3) aimed at investigating the neural basis of action and object semantic knowledge. The relevant literature provides three predominant theoretical accounts for conceptual representation of objects in the brain. According to the embodiment theories (Barsalou et al., 2003), semantic knowledge is represented in primary sensory and motor areas. Action plays a crucial role, so that when the motor system is damaged, not only is action knowledge disrupted, but the object concept is also impoverished (Gallese & Lakoff, 2005). An alternative view states that conceptual knowledge of objects is represented in multi-modal convergence areas in which various types of object knowledge derived from primary sensory and motor areas are integrated (Martin, 2016). According to this hypothesis, the posterior middle temporal gyrus (pMTG) is the convergence area representing multi-modal semantic knowledge of artifact. The pMTG is highly interconnected with neighboring sensory and motor areas, so that the degree to which a specific object property (e.g. color) is disrupted depends upon lesions in connectivity with areas that process that feature. Finally, a third theoretical perspective, namely, the “Hub & Spokes” theory, states that various types of sensory and motor knowledge converge in the bilateral anterior temporal lobes (Patterson et al., 2007). When the anterior temporal lobes are damaged, object concepts are degraded and loss of semantic knowledge emerges in every semantic task, irrespective of the semantic association that is required. In fact, patients with Semantic Dementia and bilateral anterior temporal lobe atrophy, are usually impaired in various semantic tasks, irrespective of the required semantic categorization (Jefferies & Lambon Ralph, 2006; Jefferies, 2013). To compare predictions of these three different perspectives, neurodegenerative patients and healthy participants were tested with a category decision task (see paragraph 3.2.2), and asked to decide whether two words referred to objects that could be manipulated in the same way (Manipulation), share the same function (Purpose), and be used in the same context (Context of Use). Behavioral results of single-cases illustrated that Manipulation, Purpose and Context of Use could be selectively impaired in neurodegenerative patients (see paragraph 3.3.1). Three distinct patterns of behavior were identified: a first group of patients performed equally on the three types of categorization, a second group was significantly more impaired on Manipulation, and a third group was significantly more impaired on Purpose and/or Context. It was not possible to assign a specific pattern of impairment to a diagnosis, but a selective deficit for Manipulation knowledge was detected specifically in patients with corticobasal syndrome and posterior cortical atrophy, whereas a major deficit in Purpose and/or Context condition was detected specifically in patients with Semantic Dementia (see paragraph 3.3.2). In strong contrast to what the embodiment theories predict, damage of Manipulation did not necessarily cause a deficit in other types of semantic categorization (i.e. Purpose or Context). Neuroimaging analysis (see paragraph 3.3.3) revealed that patients who did not satisfy criteria for a dissociation had significant hypometabolism in the right hemisphere. Poor performance on Manipulation, relative to Purpose or Context, was associated with the posterior middle temporal gyrus, the angular gyrus and the inferior temporal gyrus in the left hemisphere. Worse performance on Purpose and/or Context, relative to Manipulation, correlated with hypometabolism in the inferior temporal gyrus, the fusiform gyrus and the temporal pole in the left hemisphere. These results are in strong contrast with the embodiment theories, which affirm that Manipulation knowledge is represented in premotor and motor areas. Conversely, these results support other theories of semantic architecture. In fact, although patients with Semantic Dementia exhibited damage to the three types of semantic categorization, their performance on Purpose was significantly more impaired than on Context or Manipulation. This evidence is apparently in contrast with predictions made by the Hub and Spokes theory. However, behavioral patterns revealed that it was not possible to detect a completely spared performance on Manipulation when Purpose and Context were damaged. Furthermore, severe damage to Context and Purpose conditions were significantly correlated with hypometabolism in the left anterior temporal lobe. This result was even stronger in the neuroimaging analysis, which considered all patients together. Taken together, neuroimaging results suggest that damage to the left anterior temporal lobe causes significant difficulties in all types of semantic categorization, in agreement with the Hub and Spokes theory. An enlargement of the sample size in the neuroimaging analysis could provide further evidence to disentangle these contrasting outcomes.

Recently, the existence of manipulation knowledge, stored somewhere in the brain, containing information about how to correctly manipulate objects that we already know from our previous experience with them, has been questioned (Osiurak & Badets, 2016). According to these authors, manipulation knowledge may not be necessary for object use due to the fact that, when we see an object, we are able to extract the relevant mechanical and sensory properties, reason on them and solve the problem of how to use that object purposefully (Osiurak, 2014; Osiurak and Badets, 2016). In this theoretical framework, technical reasoning, rather than manipulation knowledge, has a crucial role in actual object use, and especially in those tasks that require more than one object (e.g. tool-recipient actions such as hammering a nail in a piece of wood), which are representative of everyday complex action. Conversely, according to the manipulation-based approach, information on how to manipulate familiar tools (Buxbaum, 2001) - which is stored within the ventro-dorsal stream (Buxbaum & Kalénine, 2010; Binkofski & Buxbaum, 2013; Watson & Buxbaum, 2015) - plays a crucial role in our ability to correctly use objects. A further type of semantic knowledge, i.e. knowledge about in which context and for which purpose a tool is usually used, may also support tool-object application. Specifically, in patients with manipulation knowledge deficits, intact function knowledge may help in accessing the relevant function properties of the object and understanding the purpose of use of that object.

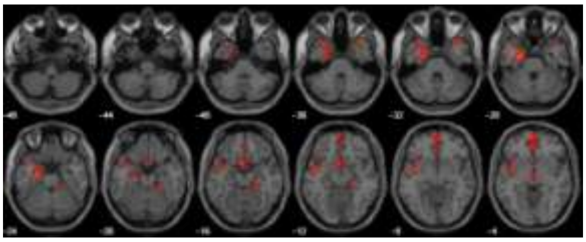
The third study in the present dissertation (chapter 4) aimed at exploring the relationship between different cognitive abilities (i.e. semantic knowledge, manipulation knowledge and praxis) in actual object use tasks. The study was ideated in collaboration with the University Clinic of Cologne. The Italian study focused on patients with Alzheimer's Dementia, who were tested with a Semantic Association Task, a Manipulation/Function task, a meaningless gestures imitation task, an apraxia battery and two actual object use tasks (see paragraph 4.2.3). Results of this third study demonstrated that defective performance in the Manipulation task significantly predicted object use deficits (see paragraph 4.3.1.4). Furthermore, residual abilities in associating objects which shared the same function significantly predicted a positive outcome in the object use tasks. Thus, function knowledge, together with other spared abilities such as technical reasoning, may allow patients to compensate for the manipulation knowledge loss and help when using objects in everyday life. These results have potential importance for the diagnosis and rehabilitation of object use disorders in patients. Traditionally, it has been suggested that apraxic patients are impaired when asked to execute gestures in testing sessions, but they are able to produce gestures correctly in ecological conditions, when they act spontaneously (Basso & Capitani, 1985; Liepmann, 1905; 1908; Trojano et al., 2007). However, other studies have demonstrated that apraxic symptoms significantly correlate with patients' ability to execute simple activities of everyday life (Hanna-Pladdy et al., 2003; Goldenberg & Hagmann, 1998b). Furthermore, when limb apraxia is not treated, it has a negative impact on rehabilitation (Basso et al., 1987). Recently, Dovern et al. (2012) have critically reviewed these issues. They highlighted that apraxia may be considered to have little impact on the patients' everyday lives because most of the neuropsychological tests used for clinical purposes (e.g. pantomiming the use of objects) seem to have no direct bearing on the actual affordances of daily life. Toward this direction, my latter study presented two new object use tasks that can be used to accurately diagnose or rehabilitate tool use deficits. Although numerous single object use tasks have been discussed in literature, many of them exhibit significant drawbacks. First, not all single object use tasks employed in other studies provide normative data on healthy participants or cut-off scores (Negri et al., 2007b). Even more frequently, there is also a lack of consistent data on patients (Bartolo et al., 2008; Zanini et al., 1999). A good examination of both patients and healthy participant was conducted by De Renzi and colleagues (1968), but their task included 5 single object and 2 multiple objects actions in the same test. Moreover, the latter actions are not easily executed with one hand only (e.g. open and close a padlock with its key). In fact, the common problem of multiple object use tasks is that they often require the use of both hands. This is a great limitation, because many patients who suffer from apraxia due to left hemisphere stroke often suffer also from hemiplegia. This means that they would not be able to use two hands. The multiple object use task that was employed in the study allowed the evaluation of 8 relatively complex actions that could be performed with one hand only. Future research will focus on stroke patients, with the aim of comparing prospective results with those already obtained on Alzeimer's Disease patients.

In conclusion, the three studies reported in the present dissertation provide new insights about the cognitive mechanisms underlying apraxia and its relationship with language. As previous studies reported (Mengotti et al., 2013, Goldenberg & Randerath, 2015; Achilles et al., 2016), cognitive mechanisms and neural regions that support the imitation of meaningful gestures may overlap with those recruited in language tasks. Specifically, in the first study reported in the present dissertation, the imitation of meaningful gestures was significantly associated with semantic processing that enables the association of objects that can be used together in the same action. This evidence suggests that the cognitive mechanism that is disrupted in patients suffering from left hemisphere stroke lesions is the access to the meaning of gestures and actions with objects. These results led us to further explore the relationship between praxis and object semantic knowledge. In particular, among all semantic features that concur to build object concepts, it has been proposed that manipulation and function knowledge play an extremely important role in object use abilities (van Elk et al., 2014; Buxbaum, 2017). Although recent studies questioned the existence of manipulation knowledge (Baumard et al., 2016; Osiurak & Badets, 2016), stored somewhere in the brain, the second study described in the present dissertation demonstrated that manipulation knowledge is distinct from other types of semantic association, such as purpose and context of use, it may be selectively impaired, and is associated with specific neural areas, such as the left inferior and middle temporal gyrus, and the left angular gyrus. Finally, the third study demonstrates that manipulation knowledge significantly predicts performance on actual tool use tasks, providing new evidence in the actual debate between the manipulation-based approach and the technical reasoning hypothesis.

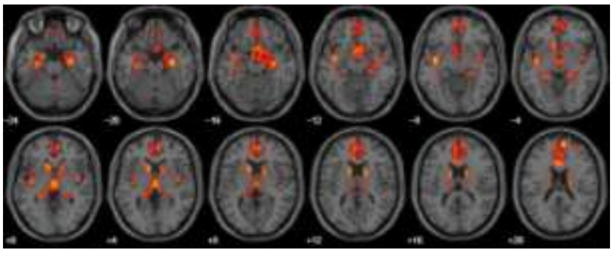
APPENDIX A.

PET images of the 17 patients included in the metabolic neuroimaging analysis in the STUDY 2. From yellow to red: areas of increasingly significant hypometabolism. Cases D.M., E.B., G.B., G.G., I.B., L.B., P.A. and S.C. belonged to the NoDiss subgroup, patients A.U., E.G.P., G.B. and P.V. belonged to the P/C<M subgroup, and patients C.C., C.D., F.C., M.R. and P.P. belonged to the M<P/C subgroup.

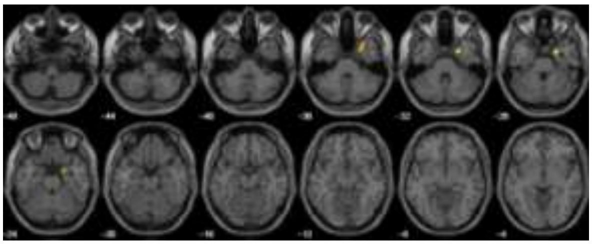
D.M.



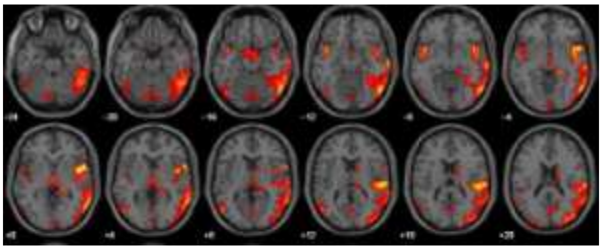
E.B.



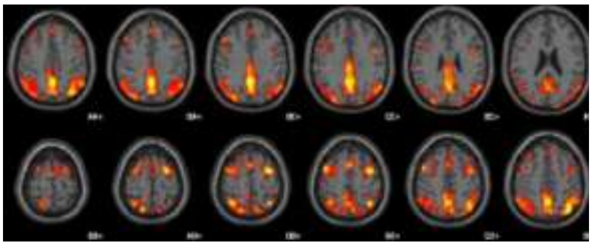
G.B.



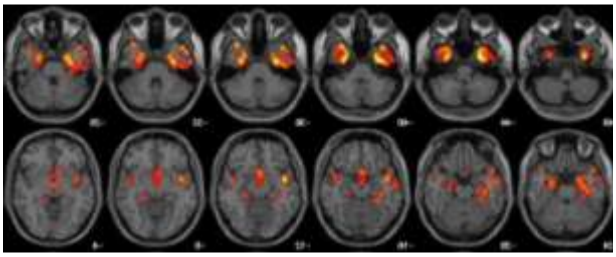
G.G.



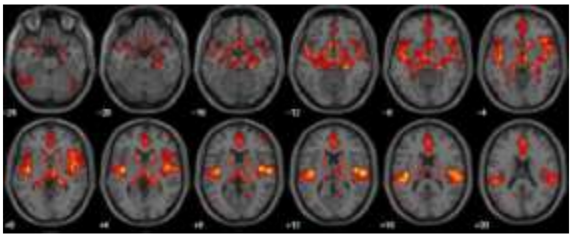
I.B.



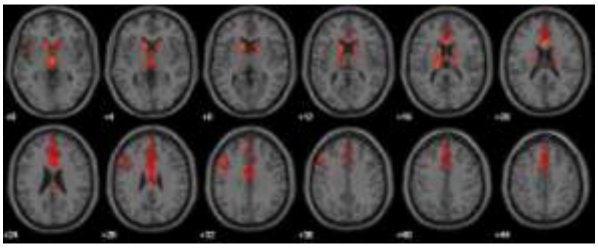
L.B.



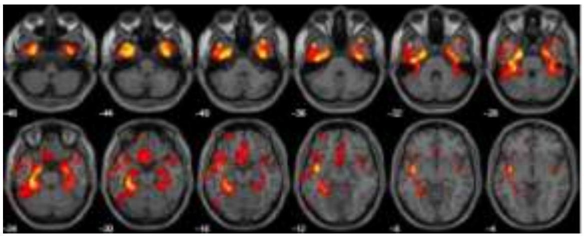
P.A.



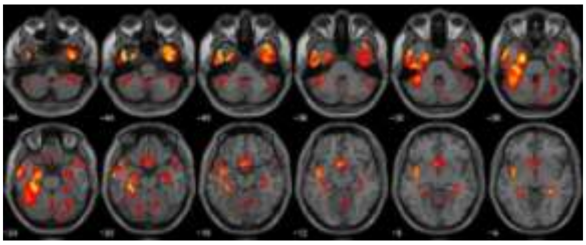
S.C.



A.U.



E.G.P



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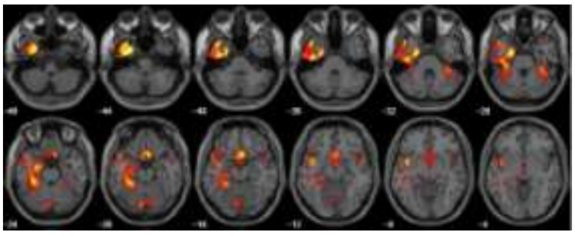

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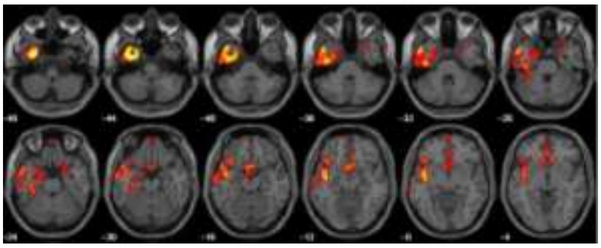
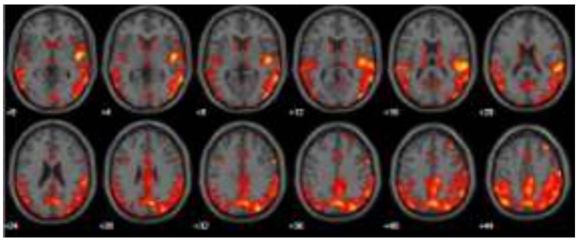
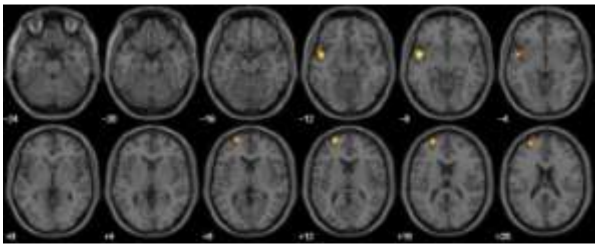


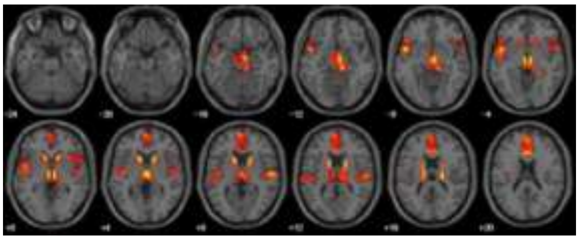
C.C.



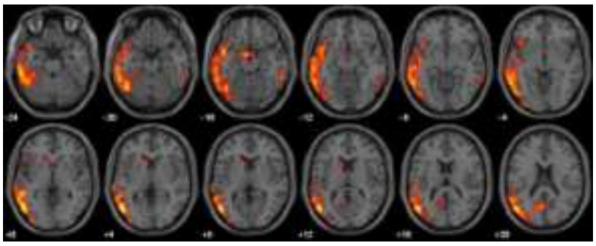
C.D.



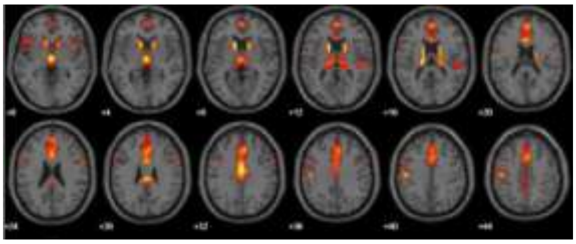
F.C.



M.R.



P.P.



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