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Did I do that?
The subjective experience of agency and its neural correlates in healthy and pathological conditions

Doctoral thesis by

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Abstract

Modifying the external world through our own voluntary actions is a fundamental aspect of human experience. In adult life, this experience also produces a peculiar feeling of controlling external events, called the "sense of agency."

Perhaps because of its elusive essence, both the subjective experience of agency and its neural correlates – although extensively investigated – remain poorly understood.

Over the past decades, new objective measures have been developed to study the sense of agency (e.g., the intentional binding effect), together with new theories emerging from cognitive and computational neuroscience. Coupled with multi-modal neuroscientific techniques, these new methods and theories create a powerful set of tools for investigating the subjective experience of agency and overcoming the limits of previous studies.

In this PhD project, I explored the sense of agency by taking advantage of the implicit index of the agency experience known as the intentional binding effect in a series of experiments with meta-analytical techniques, behavioral tasks, functional magnetic imaging, and non-invasive brain stimulation, in healthy and pathological populations.

In particular, I first reviewed the state of the art of the investigation on the human sense of agency (chapter one, introduction and meta-analytical investigation). I then characterized the neurofunctional correlates of the sense of agency (chapter two, first functional magnetic resonance imaging (fMRI) study) and determined the consequences of modulating the key nodes of the resulting putative agency brain network on the behavior (chapter three, transcranial magnetic stimulation (TMS) study). I continued exploring the effects of modulating different features of the action-outcome on the behavior and cortical activity associated with the sense of agency (chapter four, second fMRI study). Finally, I completed my investigation exploring possible aberrant agency experiences and associated neurofunctional alterations in a clinical population affected by Gilles de la Tourette syndrome (chapter five, third fMRI study).

As well as offering new insights into how we feel in control of our movements, this PhD thesis provides new chances for understanding and treating the disorders of the sense of agency and suggests a number of opportunities for future clinical and empirical works (chapter six, general discussion).

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Chapter 1

Introduction: What is the sense of agency?

In this thesis, I have investigated the meta-analytical, behavioral, and neurofunctional correlates of the sense of agency. In this opening chapter, I describe how the sense of agency is defined. I summarize how it is normally operationalized and measured in experimental laboratory settings. I then consider the different theoretical frameworks that addressed the cognitive processes that generate a sense of agency in humans. I continue exploring the brain mechanisms that underlie these processes through a meta-analytical evaluation of the existing neuroimaging literature. I end by discussing the disruptions of the sense of agency that characterize different pathological conditions, with specific reference to the movement disorders. This introduction is not meant to be exhaustive. It is instead intended to give the reader a general overview of the topic.

Definition

In social sciences, the term "agency" refers to individuals' ability to act on one's will. Therefore, one can speak about the objective facts of agency, namely the event of performing an action, from the intention to move, the motor preparation, and execution, to the appreciation of the generated consequences. Besides, the agency is also a subjective element, experience, or

"sense." The term "sense of agency" refers to this subjective experience, contrasting with the objective facts of the agency (Haggard and Eitam 2015).

The sense of agency has been defined as "the feeling of making something happen" or "the experience of controlling one's own actions and, through them, the course of events in the outside world" (Haggard 2017).

These definitions contain some of the key features of the sense of agency. One of them regards the motor act for which the sense of agency is experienced. Indeed, the sense of agency accompanies the execution of a *specific motor act*. It is then different than a set of beliefs about the feasibility of potential actions that typically designate self-efficacy (Bandura 1982). Instead, the sense of agency refers to the specific muscular movement running at that very moment and generating specific consequences in the environment.

A second crucial aspect of the sense of agency is the *voluntariness of the movement*. Precisely, the sense of agency refers to the experience or feeling that accompanies and conveys the execution of a motor act and, precisely, a voluntary, internally driven movement. Therefore, to experience a sense of agency for an action, an agent must perform the action intentionally, or the consequences that have been generated must somehow be traced back to the agent's intention.

A third aspect regards the outcome of the performed action. To feel a sense of agency, the content of the intention must produce a *specific external event*. Thus, the normal sense of agency necessarily involves the experience of an external sensory consequence, which has been achieved through one's own action. It follows that the sense of agency entails both the cognitive experience of intending and a further class of experiences associated with the body actually moving and the generated consequences in the environment. The core of the sense of agency is then the association between the intention and the outcome (Haggard 2017).

In summary, the sense of agency can be defined as the experience that occurs before, during, and after a specific voluntarily muscular movement, tying together the agent's will and the generated events in the outside world to determine an individual sense of responsibility for both the action and the following outcomes.

In recent years, it has been proposed that the so defined "sense of agency" actually entails a plurality of meanings, and the conceptual understanding of the sense of agency can be best captured by analyzing it in terms of a distinction between a "judgment of agency" and a "feeling

of agency" (Synofzik, Vosgerau and Newen 2008a). The judgment of agency refers to the conceptual, interpretative judgment of being an agent ("I did that"). It arises when the agent makes explicit attribution of agency for an action or an event to the self or other. It requires high-level cognitive processes, such as prior beliefs and conscious access to contextual information relating to the event. Instead, the feeling of agency represents the non-conceptual, low-level feeling of being the agent of an action. It represents the intangible sense of being in control of the action that flows in the background on the agent's stream of thoughts. It does not require conscious control, and it relies on low-level sensorimotor cues and contingencies (Synofzik, Vosgerau and Newen 2008b).

Importantly, explicit judgments of agency are rare in everyday life. While they might be significant in social settings where individuals may be held responsible or liable for the consequences of their behavior, the everyday experience of agency mostly relies on the implicit background feelings of being in control (Kühn, Brass and Haggard 2013). Indeed, humans constantly feel a flow between the actions they intend to perform and their external effects (Kühn et al. 2013). This makes the agency experience[1] quite thin and phenomenologically elusive (Haggard 2005), as well as challenging to study in an ecologically relevant state in the research environment.

Notwithstanding its elusiveness, the ubiquity of the sense of agency in human life is undeniable. It is involved in any exchange between the agent and the environment. It denotes the mechanism by which the self-generated stimuli can be distinguished from external-generated sensations. It contributes to people's self-awareness, allowing them to feel unique and different from others based on their behavior. It also represents the basis for developing a feeling of responsibility for the consequences of the generated actions and an essential cue for attributing legal liability (Frith 2014, Haggard 2017). In addition, it is becoming increasingly clear that aberrant experiences of agency are important features of several neurological and psychiatric conditions (Delorme et al. 2016a, Delorme et al. 2016b, Haggard et al. 2003, Moore et al. 2010b, Nahab et al. 2017, Voss et al. 2010), with major implications for quality of life. Consequently, the sense of agency has been receiving increasing attention in cognitive neuroscience research in the last two decades.

[1] It is worth nothing that, although its heterogeneous nature, for the sake of simplicity, I will use the term ''sense of agency" as a superordinate term throughout this thesis unless either the judgment or feeling level is otherwise specified.

Measures

The investigation of human self-awareness represents a longstanding endeavor in experimental psychology (see, for example, the seminal experiment of Libet et al. 1983). However, due to its elusive nature (Haggard 2005), studies on the sense of agency have faced several methodological problems in designing experimental paradigms able to capture the sense of agency in an ecologically relevant state while in a research environment.

Generally, experimental paradigms for the agency investigation can be grouped into explicit and implicit measures. Explicit measures aim to capture the conceptual, interpretative "judgment of agency." Implicit measures, like the intentional binding effect (Haggard, Clark and Kalogeras 2002) and the sensory attenuation (Blakemore, Wolpert and Frith 1998), are designed to study the elusive fundamental feeling of being the agent of an action (i.e., the "feeling of agency").

Explicit measures rest upon humans' ability to reflect on their agentic role when directly asked about it. The simplest way to ask about an individual's sense of agency is the straightforward question: "Did you do that?" (Haggard 2017). In the research environment, this simple question has been entered into complex experimental paradigms based on the so-called "action-recognition tasks." In a typical example, participants make actions without seeing their movement. Rather, they see feedback through a screen. The feedback can refer to either participant's movement or experimental manipulation of it, whereby a temporal or spatial delay is added between the real execution and that depicted on the screen. Participants are typically asked to judge whether the video they are watching is showing their own hand movements or those of another person (i.e., the experimenter), or the degree of control they experience on the seen scene. In one prototypical example, Farrer et al. (2008a) asked participants to use a joystick to perform random movements while observing action feedback in the form of a virtual hand on a monitor. The feedback could either replicate the performed movement or be characterized by temporal or spatial distortion. Participants were then asked to report whether they were viewing their actions, their movements modified, or those of the experimenter. Participants were not informed that the movement was always their own. Instead, they attributed movements to another agent when there was a high spatial discordance between participants' hand movements and sensory feedback (Farrer et al. 2008a).

Explicit measures are undoubtedly intuitive, but they can be vulnerable to consistent cognitive biases, typical of self-report measures. For example, people can overestimate their agency, claiming authorship of actions or consequences that are not their own (see, for example, Wegner and Wheatley 1999). Moreover, questions about the sense of agency may sound odd since people are not used to thinking overtly about their agentic role. Given these limits, it has been recommended that the sense of agency should be studied by implicit measures instead (Haggard 2017). Implicit measures do not imply directly asking participants about their agentic experience. Rather, they rely on unconscious biases in the behavior that provides indirect clues of people's agentic role.

A major one is the intentional binding effect (Haggard et al. 2002, Moore and Obhi 2012). In experiments focusing on the intentional binding effect, participants are usually asked to report the perceived timing of voluntary action, the timing of a subsequent sensory effect, or the elapsed time interval between them. Haggard et al. (2002) first showed that voluntary actions, but not passively induced movements, are perceived as shifted towards their effects, and their effects are shifted back towards the voluntary actions that caused them. As a result, when the action is voluntarily executed, a time compression between actions and effects is reported (2002). For a graphical representation of the phenomenon, see **Figure 1**.

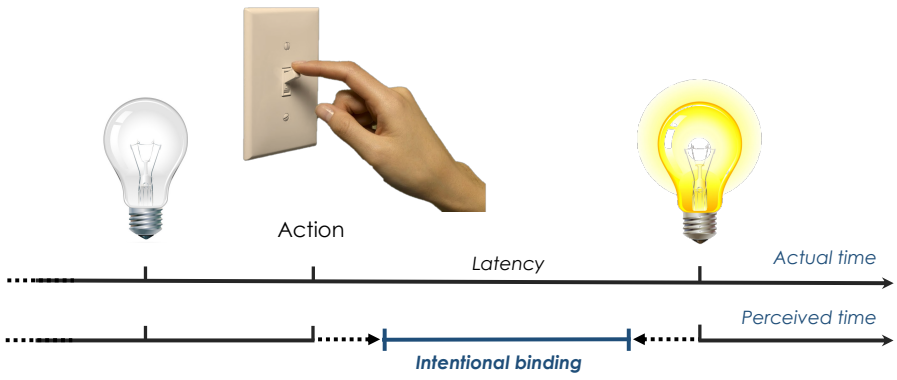


Figure 1 | The Intentional Binding effect. The intentional binding effect refers to the perceived compression of the time interval between a voluntary action (e.g., pressing the light switch to turn on the light) and its external sensory consequence (e.g., the illumination of the lamp).

The intentional binding effect has been replicated several times (see for a review Moore and Obhi 2012). It has also been generalized to actions and sensory consequences of different modalities, including auditory (Haggard et al. 2002, Jo et al. 2014), visual (Kühn et al. 2013),

and tactile outcomes (Engbert, Wohlschläger and Haggard 2008). The validity of the intentional binding as an implicit measure of the sense of agency has been ensured by the evidence that the effect results from the comparison of active versus passive movements (which serve as a baseline condition), and the time compression between acts and consequences is reported to be systematically larger for active movements. In addition, patients with a perturbed sense of agency like schizophrenic individuals show a perturbed intentional binding, providing further validation of the measure (Voss et al. 2010, Haggard et al. 2003).
At a mechanistic level, the action-effect binding has been explained as the result of the slowing down of an internal clock during the time between a voluntary action and its effects (Wenke and Haggard 2009). As a result, this imprecision in time perception permits addressing the implicit appreciation of the intentional acts and their effects. Since its seminal introduction, the intentional binding effect has become one of the most widely used implicit markers of the sense of agency (see for a review Moore and Obhi 2012).

Another implicit measure of the sense of agency is sensory attenuation. This phenomenon refers to the reduction of the perceived intensity of the afferent input of self-produced sensory effects (Bays, Flanagan and Wolpert 2006, Blakemore, Wolpert and Frith 2000). Precisely, it has been shown that humans perceive the intensity of the sensory consequences of voluntary actions as less intense than the same stimuli generated by passive movements (Blakemore et al. 1998, Blakemore et al. 2000). Blakemore et al. (2002) suggested that this bias in perception represents the mechanism by which self-generated stimuli can be distinguished from external-generated sensations. Specifically, this would happen by increasing the salience of sensations with an external cause relative to self-generated sensations (Blakemore, Wolpert and Frith 2002). It is argued that this occurs because self-generated movements involve predictive processes, in which the sensory evidence of the movement is anticipated and then partially removed from the perception (Blakemore et al. 2002). Accordingly, sensory attenuation has been widely used as an implicit marker of the sense of agency (Weiss, Herwig and Schütz-Bosbach 2011, Kühn et al. 2011). Sensory attenuation can be measured in force-matching tasks (Shergill et al. 2005). Typically, a target force is applied to the participant's hand. Participants are then required to match the force they experienced, either directly by pushing down on the same hand using their finger until they perceived the same force or indirectly by using a joystick to control the force production on the hand. Participants consistently apply a greater force when directly using their

fingers to match the externally applied target force. Conversely, they reproduce the original force much more accurately when they match the target force using the joystick. Interestingly, patients with a perturbed sense of agency have perturbed sensory attenuation. For example, schizophrenic patients match the force accurately in both conditions (Shergill et al. 2005), demonstrating that self-generated forces are less attenuated in schizophrenic patients.

Implicit measures like intentional binding and sensory attenuation have several clear advantages. First, implicit measures do not rely on subjective introspection and self-report, which might be biased or prone to the effect of confounding variables. Second, they exclude the need for metacognitive insight or self-assessing skills. This latter may be of particular relevance when studying patients with reduced metacognitive abilities, like schizophrenic patients (Kircher et al. 2007) or Parkinson's disease patients (Pareés et al. 2012). There are, however, unresolved issues with implicit measures that should also be considered. First, implicit measures are not completely free from cognitive biases. For example, implicit and explicit measures share the very same limitation known as "self-serving" bias (Bandura 1982), which can be seen in the tendency to over-attribute to oneself actions that are related to positive outcomes rather than neutral or negative (Yoshie and Haggard 2013). Furthermore, there are some intrinsic limitations of the intentional binding and sensory attenuation measures that have cast doubt on the validity of using implicit paradigms to study the human sense of agency. For example, intentional binding is usually observed on a group level, but there is a large variability between subjects. The source of this variability is largely unknown, as well as is still unknown why some individuals do not show the effect (Wolpe and Rowe 2014). Even more important, it seems to be counterintuitive that attenuating the perception of the targets of the agent's intention (i.e., the sensory attenuation phenomenon) can contribute to one's agency (Haggard 2017). This suggests that the relationship between the cancellation of reafference against predictions and the sense of agency might be more complicated than expected.

Furthermore, it also still uncertain what exactly is the relationship between implicit and explicit measures of agency in general. While it is widely accepted that there are separable, and to some extent independent, agency processing systems (Synofzik et al. 2008a), it has been shown that the two measures sometimes co-occur and sometimes dissociate (Moore et al. 2012).

Theoretical frameworks

The optimal motor control theory and the comparator model

The sense of agency is not a given. Instead, the cognitive system appears to construct it actively. Several theories have been developed to explain the origins of this elusive feeling of being the agent of an action. One prominent framework has drawn on concepts from *optimal motor control theory* (Franklin and Wolpert 2011, Wolpert and Ghahramani 2000).

Central to *optimal motor control theory* is the idea that the motor control system uses internal models, which represent the motor-to-sensory transformations and how these are implemented in the physical world (Franklin and Wolpert 2011, Wolpert and Ghahramani 2000). The control of action mainly depends on the coupling of those internal models through a series of comparators, i.e., mechanisms that compare signals and use the result of the comparison to regulate the system. There are two types of internal models: inverse and forward models. Inverse models compute the motor commands that need to be generated to change the system's actual state into the desired state. Forward models operate in the opposite direction: they represent the natural course of action and use it to predict the system's next state.

According to this framework, the course of action generation should be as follows. The action starts with an intention to achieve the desired state. An inverse model provides the motor plan necessary for achieving the desired state giving the system's current internal and external state. The plan generates the appropriate motor commands and determines the actual moving of the body. Simultaneously, a forward model uses the so-called "efference copy" of the motor plan to create predictions of the sensory consequences of performing this motor plan. Predictions are then compared with the real outcomes of the actions through a comparator (Haggard, 2017). The result of the comparison can be then used in three ways: to adjust the current motor command to rapidly correct the movements, to attenuate sensory feedbacks that are self-produced (the phenomenon known as "sensory attenuation", Blakemore et al. 2002, Frith, Blakemore and Wolpert 2000), and to attribute the agency for the generated action-outcome (Haggard, 2017). Specifically, the sense of agency arises as a result of a comparison between the predictive signals generated from the forward model during the motor planning and the actual sensory effect of one's action (hence the name "Comparator Model", Blakemore et al. 2002, Frith et al. 2000). An action is perceived as self-caused when there is a match between

the predicted and experienced sensory effects (Frith et al. 2000). Instead, any discrepancy generates a prediction error, and the action is perceived as externally generated, i.e., independent of one's own volition (Haggard 2017). See **Figure 2** for a graphical representation of the model.

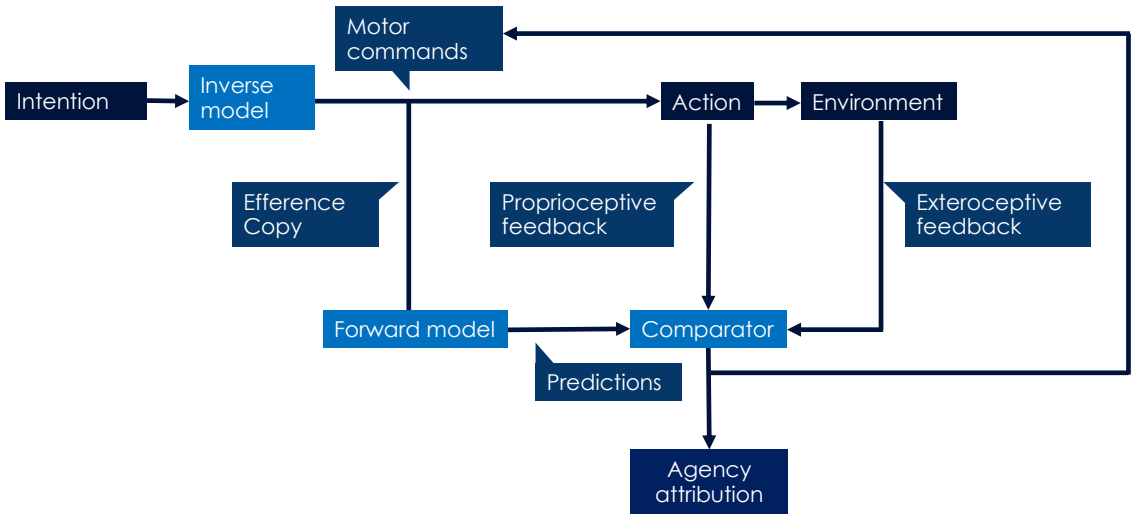


Figure 2 | The basic components of the Comparator model for the sense of agency. Adapted from Haggard 2017.

A large body of evidence has suggested that the sense of agency, especially for what concerns the judgment of agency, strongly depends on the degree of congruence between predicted and actual sensory outcome. For example, as mentioned before, Farrer et al. (2008a) showed that people attributed movements to another agent when there was a spatial discordance between their own hand movements and sensory feedback (Farrer et al. 2008a).

In addition, the comparator model first described some important aspects of the agency experience, which are today widely accepted. Among these, this framework specifically emphasizes the role of predictive signals for the sense of agency, which importance has also been recognized by the newest models of motor control and agency (Friston, Mattout and Kilner 2011). However, it has been increasingly clear that a simple comparison fails to account for all features of the subjective experience of one's own agency. For example, according to the comparator model, the sense of agency is caused by the lack of any prediction error. The model would not produce any signal when there is a match between an intention and its expected consequence. Therefore, it has been discussed that while the comparator model may

successfully explain the 'non-agency' phenomenon, it fails in describing the "positive" experience of agency (Haggard 2017). Moreover, according to the model, the arising of the sense of agency is delayed in time compared to the time of action: it cannot be computed until the predictions are compared with the delayed outcome feedback. This implies that people would experience a sense of agency after the event (Haggard 2017). However, this collides with evidence showing that the sense of agency can be felt even when the action produced no effect in the external environment. For example, Moore and Haggard (2008) showed that when the predictability of the effect of the action is high, temporal binding can occur even when the action produced no consequence (Moore and Haggard 2008). Furthermore, it has been argued that people can sometimes attribute actions to themselves despite a mismatch between the predicted and actual outcomes (Synofzik et al. 2008a). Experimental studies have shown that, within a certain range (up to 15° in space or 150ms in time), distorted sensory consequences can be experienced as self-generated, despite the underlying mismatch at the comparator (Daprati et al. 1997). Finally, there are cases in which the comparator is not required for the arising of the sense of agency (Synofzik et al. 2008a). For example, it has been shown that awareness and attribution of agency can rely on higher-order causal inferences between thoughts and actions on the basis of belief states, even when the beliefs are wrong (Wegner and Wheatley 1999, Wegner 2003).

From the Apparent Mental Causation theory towards an integrative approach

This latter evidence has led to the formulation of the "apparent mental causation" theory (Wegner 2003), which describes the experience of agency as a retrospective insertion to consciousness or a post-hoc reconstruction of events and their likely causes (Wegner and Wheatley 1999). In their seminal study, Wegner and Wheatley (1999) showed that priming participants with cues consistent with the action-outcomes encouraged participants to attribute actions to themselves, even when they did not perform the action at all (Wegner and Wheatley 1999). In other words, primes were able to modulate the participants' feeling of control over movements they did not make, inducing a false sense of agency for movements that participants had, in fact, not performed. The easily biased nature of the sense of agency was taken as evidence that the agency experience arises from an inferential sense-making process drawn after the end of the movement, rather than from predictive processes. In other words, the agency

experience would arise when the agent infers an apparent causal path from thought to action. According to this view, both thought and action are actually caused by some unconscious mental events, which might also be connected to each other, directly or through other mental processes. The actual causal paths are not present in the person's consciousness. Instead, they are reconstructed through an inferential process. The sense of agency is then experienced as a result of what is apparent, not what is real (hence the name "Apparent Mental Causation theory", Wegner 2003). Wegner (2003) also suggested that the inference occurs in accordance with three main principles: priority, consistency, exclusivity: if (1) a thought becomes conscious just before an action (priority), (2) the thought is consistent with the action (consistency) and (3) it is not accompanied by apparent alternative causes of the action (exclusivity), the agent experiences conscious intention and ascribes the generated sensory consequences to her/his own action. See **Figure 3** for a graphical representation of the Apparent Mental Causation theory.

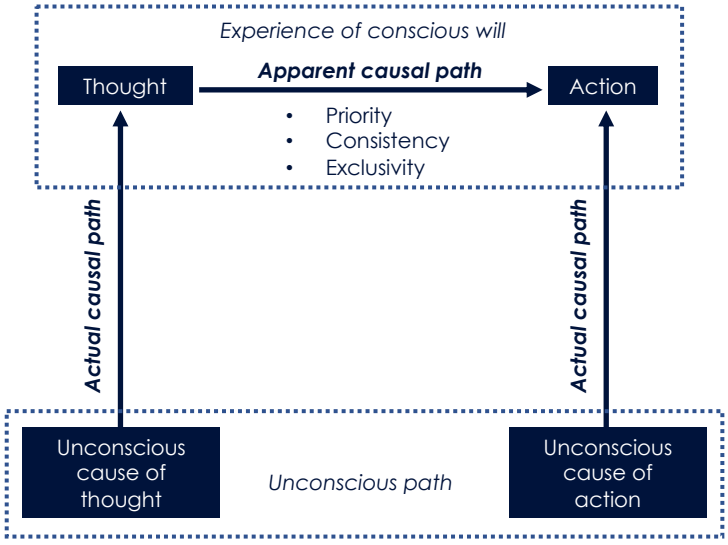


Figure 3 | Graphical representation of the experience of conscious will according to the Apparent Mental Causation theory. Adapted from Wegner and Wheatley (1999).

In essence, the comparator model and the apparent mental causation theory differ according to whether the sense of agency relies on internal or external cues. The comparator model claims the importance of internal predictive signals. The apparent mental causation theory highlights the role of higher-level external, situational cues for the attribution of self-generated consequences to the self of others.

More recently, this dichotomy has been overcome by the proposal that several sources of information can contribute to the emergence of the sense of agency (Moore, Wegner and Haggard 2009, Synofzik et al. 2008a, Wolpe et al. 2013). Synofzik et al. (2008a) first proposed a two-step account of agency in which the feeling of agency derives from a weighting process of different action-related perceptual and motor cues, and the judgment of agency arises from conceptual skills and attitudes (e.g., beliefs, desires) and social and contextual cues. The extent to which the feeling and judgment of agency contribute to the overall sense of agency then depends on the context and results from the integration of all the multiple, internal and external, cues (Synofzik et al. 2008a). See **Figure 4** for a graphical representation of the two-step account of agency.

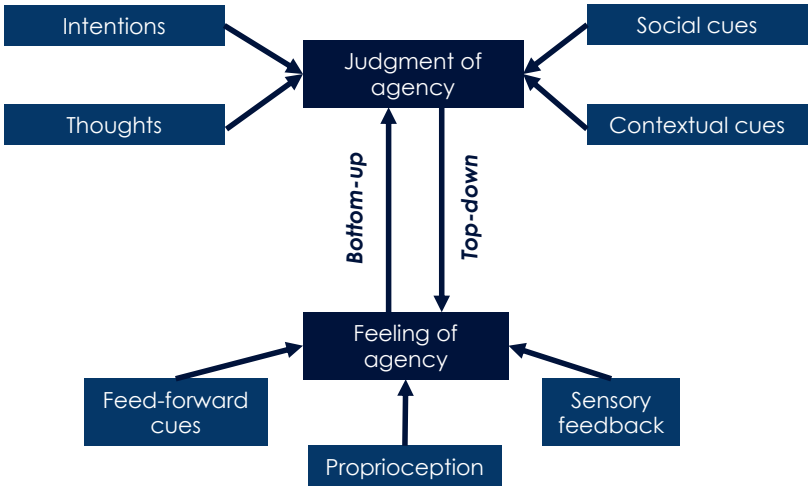


Figure 4 | Graphical representation of the two-step account of agency by Synofzik et al. Adapted from Synofzik et al. (2008a).

Moore et al. (2009) then expanded Synofzik's (2008a) proposal by suggesting that the relative influence of the different information sources may be linked to their reliability, with the more reliable source of information dominating the agentic experience. They proposed a form of optimal cue integration based on established models in human perception, which was called "cue integration theory" (Moore et al. 2009).

Support to this theory comes, for example, from a study by Desantis et al. (2011). They found increased intentional binding when participants were led to believe that their own behavior caused the outcome compared to the condition in which they believed that the experimenter caused the effect, supporting the significant role of high-level beliefs and external cues in the

sense of agency generation. However, they also found a normal binding in the uncertain condition where participants were unsure whether they or the experimenter had produced an outcome. These results suggest that participants use sensorimotor information to guide their experience of action when receiving uncertain external cues, suggesting that internal cues to agency receive higher weighting in the absence of any reliable external information (Desantis, Roussel and Waszak 2011).

However, although there is convincing evidence that the sense of agency can be characterized in terms of a weighted integration of internal and external cues, the cue integration approach lacks a plausible explanation of how the integration occurs in terms of underlying mechanisms.

New hints from the active inference theory

A new appealing mechanistic account of the sense of agency experience comes from the active inference framework. Active inference theory builds on the free energy principle (Friston 2010), which describes the tendency of a system to minimize the free energy of its generative model, its "entropy", or more simply the "surprise" associated with a sensation and its predicted cause (Friston et al. 2011). Accordingly, the brain uses an internal "generative model", which combines prior beliefs and sensory information to infer the cause (hidden states) of a given observation or stimulus. The theory uses principles of Bayesian statistics to integrate the dynamic comparison between the model's predictions and sensory evidence. Any discrepancy between the prior beliefs or predictions and sensory inputs produces a "prediction error", which corresponds, in the context of motor control, to the amount to unexpected proprioceptive and exteroceptive sensations that are contingent on one's action. The theory attempts to expand from behavior to neuronal and brain functions, proposing that the cerebral cortex, as well as the larger-scale organization of different brain networks, is hierarchically organized. The upper levels represent abstract, high-level, domain-general, multi-modal beliefs. Intermediate levels contain modality-specific beliefs and that increasingly relate to sensations. Lower levels address specific predictions for specific sensations, like immediate proprioceptive predictions. At each level, there is a set of neurons encoding predictions, and another set encoding prediction errors. Neuronal representations at higher levels of the hierarchy generate predictions about representations at lower levels (hence the term "generative model"). At each level within the hierarchy, descending predictions are compared with lower-level representations to form a

prediction error. Prediction error minimization can occur by 1) updating the predictions (prior beliefs), so that predictions match the actual sensory inputs or 2) generating movement by employing the proprioceptive predictions, so that the actual inputs match the predicted sensory inputs. Crucially, the mechanism by which the prediction error is resolved (changing predictions or changing sensory evidence through actions) is determined by the relative precision-weighting of predictions and prediction errors, with the more precise source of information dominating the agentic experience. Predictions that initiate a movement prevail when the precision of the current somatosensory state is down-weighted relative to predictions (Brown et al. 2013). Precision is proposed to be encoded by synaptic gain, i.e., the inverse of the variance in the fluctuation of neuronal activity. In turn, these modulations in synaptic gain are thought to underlie the physiological sensory attenuation seen prior to and during the movement in the somatosensory cortex (Brown et al. 2013).

Within these processes, the active inference theory suggests that the sense of agency depends on the capacity of higher intentional levels of the cortical hierarchy (e.g., pre-SMA and pre-frontal regions) to predict sensory data from lower levels (SMA, M1) through movement (Wolpe and Rowe 2014). Sense of agency is implicit in the cycle of active sampling of sensations, whereby the sense of agency is thought to emerge from the successful balancing of the precision of prediction errors within the cortical hierarchy for action, and the ability of this balanced hierarchy to converge on the most likely cause of a self-generated sensation, i.e., the agent himself. Active inference approaches thus the study of the sense of agency by reducing it to an active inference problem (Friston et al. 2013), where the inference that has to be made by the agent corresponds to the estimation of the probability that one was the agent of the action ("who is the agent that is minimizing the free energy?") given the sensory attributes of that action (proprioception, sensorimotor feedback, external cues) and the prior probability that the action was indeed executed by the agent (i.e., the probability that agent was optimal in minimizing the free energy associated with the desired outcomes of its actions).

Although the active inference principles have not yet been experimentally applied to the study of agency, this theory is a promising candidate to accommodate within the same framework hints from the comparator model (Frith et al. 2000, Wolpert and Ghahramani 2000), and the cue integration theory (Moore et al. 2009), while providing additional mathematical tools to develop, test, and verify theoretical and experimental hypotheses. In particular, in terms of

active inference, the proposed integration of cues externally and internally generated (Moore et al. 2009) is solved by the same generative model and by the dynamic updates of its priors. See **Figure 5** for a graphical representation of the model.

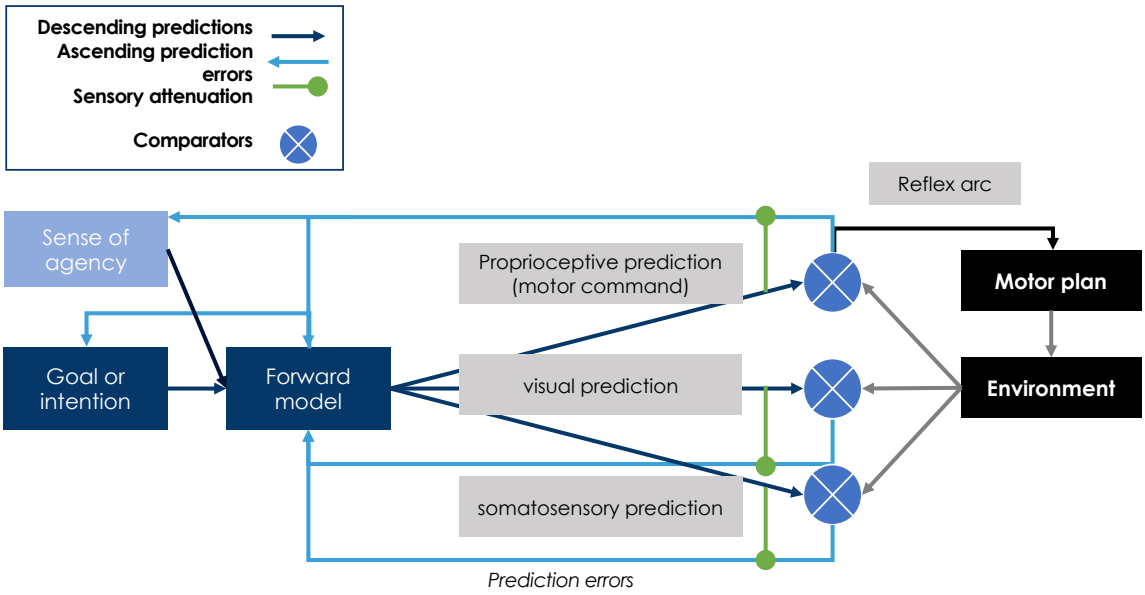


Figure 5 | Graphical representation of the active inference model for the sense of agency, adapted from Friston (2020, personal communication).

Neural mechanisms

In the past two decades, the brain mechanisms underlying the sense of agency have been extensively investigated through neuroimaging, non-invasive brain stimulation (NIBS), and electrophysiological studies.

At least nineteen neuroimaging studies have explored the neurofunctional correlates of the sense of agency in healthy adult participants. All those studies used different agency measures, multiple experimental paradigms, and distinctive imaging methods, making it difficult to draw firm conclusions. For a synopsis of neuroimaging studies on the sense of agency, see **Table A1** in the *Appendix*. For this reason, I figured that the reader might benefit from a systematic review of the existing neuroimaging literature on the sense of agency. As a consequence, in what follows, I introduce a formal meta-analysis of neuroimaging studies that aims to define the state of the art of the investigation on the neural correlates of the sense of agency.

At least nine non-invasive brain stimulation studies investigated the neural structures that play a major role in the sense of agency generation in healthy adult subjects. For a synopsis of non-invasive brain stimulation studies on the sense of agency, see **Table A2** in the *Appendix.* Seven studies used transcranial magnetic stimulation (TMS) protocols, while three preferred transcranial direct current stimulation (tDCS) protocols. Such a limited number of studies does not permit a meta-analytical evaluation of the results, especially considering that six studies targeted the parietal lobule (MacDonald and Paus 2003, Preston and Newport 2008, Ritterband-Rosenbaum et al. 2014, Chambon, Moore and Haggard 2015, Khalighinejad and Haggard 2015, Hughes 2018), three studies chose the premotor cortex as stimulation site (Moore et al. 2010a, Weiss et al. 2014, Cavazzana et al. 2015) and two studies targeted the dorsolateral prefrontal cortex (Chambon et al. 2015, Khalighinejad and Haggard 2015). However, these results can still make an important contribution to discussing the meta-analytical results from neuroimaging studies.

It is worth noting that a large corpus of studies investigating the neurobiological correlates of the sense of agency taking advantage of neurophysiological techniques like electroencephalography (EEG) and magnetoencephalography (MEG). Although important and relevant for the understanding of the human sense of agency, those results are not presented in this thesis, mainly because most EEG-MEG investigations on the human sense of agency used sensory attenuation as a measure of agency (see, for example, Martikainen, Kaneko and Hari

2005, Baess et al. 2011). However, as mentioned before, using sensory attenuation as an index of the subjective experience of agency is controversial. More recently, new methods, like subliminal priming, have given EEG studies the impulse to study the sense of agency with a new powerful set of tools for understanding human agency and its electrophysiological correlates. For example, Sidarus et al. (2017) used event-related potentials (ERPs) and subliminal priming to manipulate the fluency of selecting a left- or right-hand action in response to a supraliminal target to clarify the neural mechanisms underlying the sense of agency. They observed that both feedback-related negativity evoked by the outcome and more negative ERPs immediately after the action were associated with reduced agency ratings over action outcomes. According to the authors, these ERP components may reflect brain processes underlying prospective and retrospective components of sense of agency respectively (Sidarus, Vuorre and Haggard 2017), providing support for the "cue integration theory" (Moore et al. 2009). However, although those results are promising, they can tell nothing about the localization of these processes in the brain. Identifying the brain areas responsible for the sense of agency generation is instead the primary concern of neuroimaging studies, as well as the present thesis.

Meta-analytical review

As anticipated in the previous paragraph, several neuroimaging studies have explored the neurofunctional correlates of the sense of agency, using different agency measures, multiple experimental paradigms, and distinctive imaging methods. In what follows, I introduce a formal meta-analysis of previous neuroimaging studies that aims to test the validity of the functional anatomical assignations in terms of their replicability across studies and dissociability along the self/external agency axes. In particular, I defined as "self-agency" the experience of being in control of the action, and as "external agency" the experience of losing control over the action and the corresponding outcomes.

Methods

I identified neuroimaging studies exploring the neural correlates of the sense of agency using the following procedure. I interrogated PubMed (www.pubmed.com) in January 2020 by using the search terms: "agency" OR "sense of agency" AND "magnetic resonance imaging" OR fMRI OR "positron emission tomography" OR PET. Studies on patients, as well as studies on children and elderly subjects, were not included. Moreover, I excluded studies in which the results were not reported using standard Talairach (TAL) or Montreal Neurological Institute (MNI) coordinates. Furthermore, studies performed before January 2000 were not included, since the meaning of the sense of agency, as well as the methods of the neuroimaging techniques, may have been different earlier and may not ensure comparable results. Finally, I excluded studies in which the factors of interest for the current meta-analysis (self-agency vs. external agency) were not appropriately orthogonalized. After removing duplicates, I performed a preliminary selection based on the titles and abstracts of the papers, through which I excluded the studies that did not match the inclusion criteria. I then performed a meticulous inspection of the resulting manuscripts applying the aforementioned inclusion criteria in detail. I included activation foci resulting from simple comparisons between the factor of interest and the control condition (i.e., self-agency vs. baseline condition or external agency vs. baseline condition), direct comparison between the factors of interest (i.e., self-agency vs. external agency and vice versa), as well as from parametric regressions (e.g., the parametric function of the BOLD response as a function of the degree of self-agency).

The final *self-agency* dataset included 13 papers, 14 contrasts, and 105 activation foci. Most studies engaged participants in action recognition tasks where the visual feedback of the performed movements was artificially manipulated to either match or mismatch the participant's motor intention (Farrer and Frith 2002). They typically compared visuomotor congruency conditions (self-agency condition) with visuomotor discrepancy conditions (external-agency condition).

Since only one study took advantage of the intentional binding effect (Kühn et al. 2013), for the sake of the dataset homogeneity, I excluded it from the meta-analysis. For more details about the included studies, see **Table 1.**

Table 1 | Studies included in the meta-analysis for the self-agency factor.

Study			
Authors and year	**N**	**Imaging Method**	**Contrast Description**
Farrer & Frith (2002)	12	fMRI	Self-agency vs. control condition; Self-agency vs. external agency
Farrer et al. (2003)	8	PET	Parametric function of visuo-motor congruency degree (congruency = self-agency; no congruency = external agency)
Leube et al. (2003a)	18	fMRI	Negative correlation with visuo-motor congruency degree (congruency = self-agency; no congruency = external agency)
Leube et al. (2003b)	6	fMRI	Visual feedback of own actions (self-agency) vs. visual feedback of external's actions (external agency)
Matsuzawa et al. (2005)	6	fMRI	Visuo-motor congruency (self-agency) vs. rest
David et al. (2007)	14	fMRI	(Congruent judged as self-generated + Incongruent judged as self-generated) - (Incongruent judged as Other generated + Congruent judged as Other generated)
Schnell et al. (2007)	15	fMRI	Visuo-motor congruency (self-agency) vs. visuo-motor discrepancy (external agency)
Kontaris et al. (2009)	11	fMRI	Compatible (self-agency) vs. incompatible visual feedback (external agency)
Spengler et al. (2009)	18	fMRI	Parametric function of visuo-motor congruency degree (self-agency)
Chambon et al. (2013)	22	fMRI	Compatible action priming (self-agency) vs. not compatible action priming (external agency)
Fukushima et al. (2013)	17	fMRI	Judgment of self-agency vs judgment of external agency
Renes et al. (2015)	23	fMRI	Self-agency vs. external agency
de Bézenac et al. (2016)	24	fMRI	Main effect of self-agency condition

The final *external agency* dataset included 14 papers, 16 contrasts, and 138 activation foci. Several studies compared visuomotor discrepancy conditions (external agency condition) with visuomotor congruency conditions (self-agency condition) (David et al. 2007, Schnell et al. 2007); others explored brain regions that show a positive correlation with the extent of the discrepancy between movement and feedback (external agency condition) (Farrer et al. 2003, Leube et al. 2003b, Leube et al. 2003a). No study has taken advantage of implicit measures of agency, like intentional binding, for exploring the neural correlates of the external agency. For more details about the included studies, see **Table 2.**

Table 2 | Studies included in the meta-analysis for the external agency factor.

Study			
Authors and year	**N**	**Imaging Method**	**Contrast Description**
Farrer & Frith (2002)	12	fMRI	External agency vs. control condition; External agency vs. self-agency
Farrer et al. (2003)	8	PET	Parametric function of visuo-motor congruency degree (congruency = self-agency; no congruency = external agency)
Leube et al. (2003a)	18	fMRI	Positive correlation with visuo-motor congruency degree (congruency = self-agency; no congruency = external agency)
Leube et al. (2003b)	6	fMRI	Visual feedback of external's actions (external agency) vs. visual feedback of own actions (self-agency)
Matsuzawa et al. (2005)	6	fMRI	Visuo-motor incongruency
Balslev (2006)	15	fMRI	Asynchronous vs synchronous stimulation.
David et al. (2007)	14	fMRI	Incongruent feedback - Congruent feedback
Schnell et al. (2007)	15	fMRI	Visuo-motor discrepancy (external agency) vs. visuo-motor congruency (self-agency)
Farrer et al. (2008)	12	fMRI	External agency vs. control condition; External agency vs. self-agency
Kontaris et al. (2009)	11	fMRI	Incompatible (external agency) vs. compatible visual feedback (self-agency)
Spengler et al. (2009)	18	fMRI	Parametric function of visuo-motor incongruency degree (external agency)
Yomogida (2010)	24	fMRI	Agency violation vs. sensory match violation.
Nahab (2011)	20	fMRI	Parametric increase with to the loss of sense of agency
Fukushima et al. (2013)	17	fMRI	Judgment of external-agency vs judgment of self-agency

I performed two separate analyses for self- and external agency, respectively. Analyses were performed using activation likelihood estimation (ALE), implemented in GingerALE 3.0.2 (Eickhoff et al. 2009, Turkeltaub et al. 2012), with the Turkeltaub Non-Additive method (Turkeltaub et al. 2012). The coordinates were converted from Talairach to standard MNI space

if needed. Statistical significance was assessed with a voxel-level threshold of $p < 0.001$, and a cluster-level threshold of $p < 0.05$ corrected with Family-Wise Error (FWE), and 1000 permutation tests (Eickhoff et al. 2009, Turkeltaub et al. 2012). The maps of the ALE values were overlaid on a ch2better.nii.gz template using MRIcron software (Rorden and Brett 2000).

Results

The results of the meta-analysis evidenced one cluster of activation, located in the left posterior insula (that extends to the left putamen) that showed a significant association with the self-agency (local maximum: x= -38 y= 0 z= -2, ALE score=0.01, $p < 0.05$ corrected with Family-Wise Error (FWE), Z=3.99). See **Table 3** and **Figure 6**.

Table 3 | Results of the meta-analysis for the self-agency. For each cluster, I reported the cluster number (#), the ALE score, the centroid coordinates in the MNI stereotaxic space and the associated Z score. All clusters are significant at $p < 0.05$, corrected with Family-Wise Error (FWE)

Cluster	#	x	y	z	ALE	Z	#	x	y	z	ALE	Z
Posterior Insula							1	-38	0	-2	0.01	3.99
Putamen							1	-28	0	0	0.01	3.99

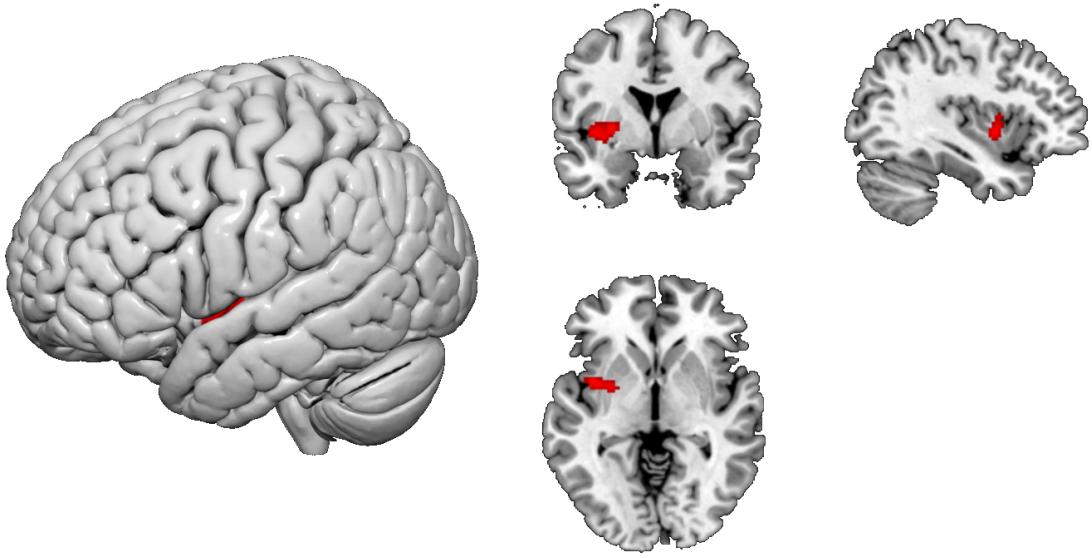


Figure 6 | Cluster of activation showing significant association with the self-agency experience.

Two clusters of activation showed a significant association with the external agency. The first cluster is located in the left inferior parietal lobule (local maximum: x= -44 y= -50 z= 44, ALE score=0.02, $p < 0.05$ corrected with Family-Wise Error (FWE), Z=5.14). The second cluster includes the right superior temporal gyrus, the right inferior parietal lobule, and extends to the right angular gyrus and the right supramarginal gyrus (local maximum: x= 58 y= -46 z= 20, ALE score=0.02, $p < 0.05$ corrected with FWE, Z=4.00). See **Table 4** and **Figure 7**.

Table 4 | Results of the meta-analysis for the external agency. For each cluster, I reported the cluster ID (#), the ALE score, the centroid coordinates in the MNI stereotaxic space and the associated Z score. All clusters are significant at $p < 0.05$, corrected with Family-Wise Error (FWE)

Cluster	#	x	y	z	ALE	Z	#	x	y	z	ALE	Z
Inferior parietal lobule (40)							1	-44	-50	44	0.02	5.14
							1	-52	-50	52	0.02	5.09
Inferior parietal lobule (40)	2	62	-50	40	0.01	3.82						
Supramarginal gyrus	2	56	-42	34	0.01	3.48						
Superior temporal gyrus	2	58	-46	20	0.01	4.00						
	2	56	-54	24	0.01	3.67						
	2	64	-54	22	0.01	3.35						
Middle temporal gyrus (21)	2	62	-50	14	0.01	3.32						

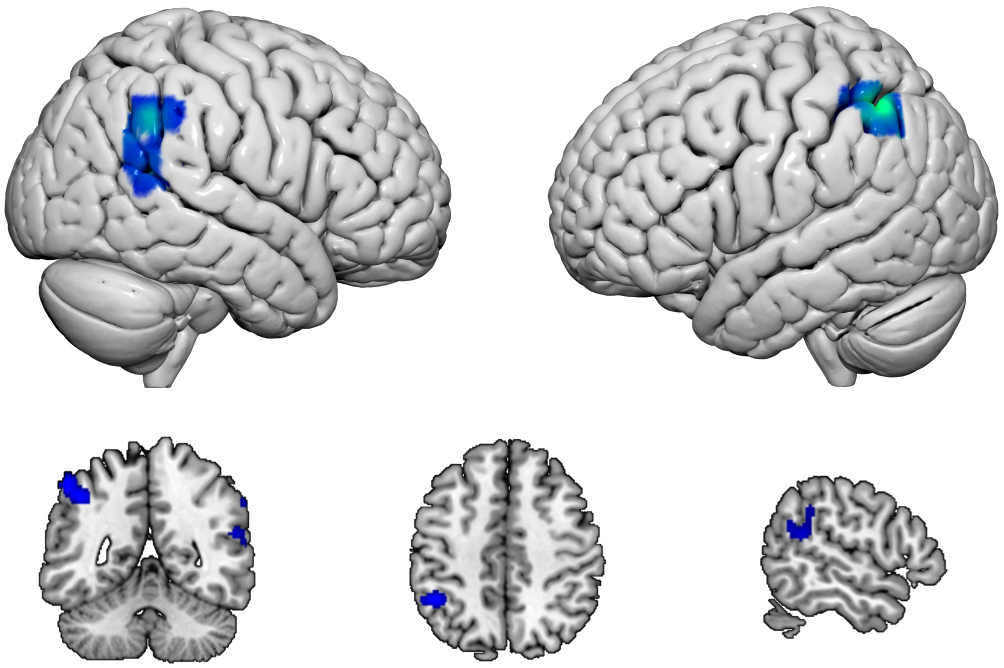


Figure 7 | Clusters of activation showing significant association with the external agency experience.

Discussion

Neuroimaging studies have consistently highlighted the role of the parietal cortex in attributing agency. Most of these studies used explicit agency-attribution judgments in action recognition tasks, in which spatial or temporal distortion was added between participants' movement and the provided visual feedback. They consistently showed the activation of the inferior parietal cortex and the angular gyrus in conditions in which visual feedback was judged as not-self-generated, unrelated to participants' intention ("External-agency" condition, see for example Farrer and Frith 2002, Farrer et al. 2003, Farrer et al. 2008b). For example, in an early study, attributing action feedback to an external agent was associated with the activation of the inferior parietal cortex (Farrer and Frith 2002). Likewise, right angular gyrus activity correlated with the magnitude of the discrepancy between the intended and the actual consequence of the action (Farrer et al. 2003). The link between the parietal lobules and the sense of agency attribution has been extensively demonstrated also by NIBS studies. For example, Preston et al. (2008) showed that participants were more likely to erroneously misattribute agency to the computer compared to the self when TMS was applied over the inferior parietal cortex (Preston and Newport 2008). Similarly, Ritterband-Rosenbaum et al. (2014) showed that - following inferior parietal cortex rTMS stimulation - subjects showed the tendency to experience self-controlled movements as being externally perturbed (Ritterband-Rosenbaum et al. 2014). In another study, Chambon et al. (2015) demonstrated that TMS over the inferior parietal cortex at the time of action selection disrupts perceived control over subsequent effects of the action (Chambon et al. 2015).

However, it is still unclear whether the parietal activations reflect the proper agency attribution process or a more general judgment that the event is externally generated (Haggard 2017). Interestingly, the temporoparietal junction also responds to unexpected external sensory stimuli, like targets at unattended locations, in the absence of any voluntary action (Kincade et al. 2005).

Moreover, while there is a cautious consensus on the structures involved in external-agency attribution, results concerning self-agency attribution are more controversial. The only area consistently associated with the self-agency attribution was the posterior insula ("Self-agency condition, see for example Farrer and Frith 2002). This result is also confirmed by a recent meta-analysis and resting-state functional connectivity study, in which I showed that posterior and anterior insular cortices differ for their functional association with the sense of agency and

intentionality, respectively (Seghezzi et al. 2019). However, the role of the insula in the genesis of the sense of agency is still unclear. One possibility is that insular activations are associated with a general multi-sensory integration process (Kurth et al. 2010b) supporting the sense of agency, rather than a specific and exclusive process that generates the proper sense of agency.

More recent evidence using implicit measures of agency has suggested that also the frontal lobe may contribute to the sense of agency generation. For example, in an event-related functional MRI study, Kühn et al. (2013) used the intentional binding effect as a proxy for the sense of agency investigation[2]. They showed that the Supplementary Motor Area (SMA) was more strongly associated with the perceived action-tone binding in an active condition than in a passive condition (Kühn et al. 2013). There is other evidence of a link between the SMA, with particular reference to its anterior portion, and the sense of agency. A resting-state functional imaging study with patients with corticobasal syndrome showed that functional connectivity patterns between the anterior portion of the SMA (pre-SMA) and the prefrontal cortex in resting conditions change according to the intentional binding effect (Wolpe et al. 2014). In addition, non-invasive brain stimulation evidence suggested that transcranial direct current stimulation over the pre-SMA reduces the intentional binding effect towards auditory outcomes (Cavazzana et al. 2015). In another study, continuous theta-burst stimulation over pre-SMA was shown to reduce the temporal linkage between a voluntary key-press action and a subsequent electrocutaneous stimulus (Moore et al. 2010a). Furthermore, EEG evidence showed that self-initiated movements following early readiness potentials - which has been related to the activity of the pre-SMA (Shibasaki and Hallett 2006) - result in a stronger binding effect compared to positive potentials (Jo et al. 2014).
However, the contribution of frontal and prefrontal lobes to the sense of agency remains controversial, since the only neuroimaging study to show a significant association between the agency measure and local brain activity in SMA applied a small volume correction in a very circumscribed area (Kühn et al. 2013). Furthermore, a crucial limit in previous NIBS studies showing the causal effect of pre-SMA stimulation on intentional binding effect was that the TMS target area was often identified from existing literature. For this reason, the authors could not ensure that the stimulated area was the same area responsible for the cognitive function

[2] It is worth noting that this study was excluded from the meta-analysis for the huge dissimilarity in the methods with respect to the other included studies.

being tested (Moore et al. 2010a, Cavazzana et al. 2015). Crucially, while Kühn et al. (2013) suggested the association between intentional binding effect and SMA activity (Kühn et al. 2013), many tDCS/TMS studies identified the pre-SMA as the target of the stimulation (Moore et al. 2010a, Cavazzana et al. 2015). However, although the spatial contiguity, SMA and pre-SMA differ widely for both anatomical and functional properties. For example, SMA is somatotopically organized, and it projects directly to the primary motor cortex (M1) and spinal cord (He, Dum and Strick 1995), and it is functionally connected with regions related to simple motor control (Kim et al. 2010). Pre-SMA is strongly connected with prefrontal cortices and high-level motor areas, and it has a specific role in the performance of complex tasks, such as the alternation of motor plans, task switching, acquisition of new motor skills, and motor selection (Nachev et al. 2007, Nachev, Kennard and Husain 2008). Therefore, while current evidence strongly supports a dissociation between external agency attribution and a sense of agency proper (or self-agency attribution), the brain areas involved in the latter process are still a matter of debate.

Pathological sense of agency

Beyond the endeavor to explain the neural basis of the sense of agency, there is also considerable interest in describing its dysfunctions. Disturbances of the sense of agency might have a deep impact on an individual's social functioning as observed, for instance, in the pathological condition of schizophrenia. Passivity phenomena in schizophrenia clearly implicate the misattribution of thoughts or actions to an external agent (Synofzik et al. 2010). In delusions of motor control, the individual firmly believes that his own action has been initiated and controlled by another agent. Similarly, in thought insertion, thoughts are perceived as externally generated, as they have been inserted in the patient's mind without permission. Experimental research on individuals with schizophrenia has confirmed that disturbances of the sense of agency characterize schizophrenic patients' life. For example, in one early study, Daprati et al. (1997) required schizophrenic patients with and without hallucinations and/or delusional experiences to perform simple finger and wrist movements without directly seeing their hands. Instead, they saw the image of either their own hand or the experimenter's hand executing the same or a different movement on a TV-screen in real-time. The task was to report whether the hand on the screen was their own or not. Compared with controls, patients made more errors in attributing actions to their correct source when the experimenter performed the same movements as them and tended to misattribute the experimenter's hand to themselves (Daprati et al. 1997). Another line of evidence comes from experiments using intentional binding. For example, Haggard et al. (2003) showed that schizophrenic patients presented an unusually strong binding effect between actions and consequences (Haggard et al. 2003). This suggests that they may over associate their actions with subsequent events, experiencing an abnormally strong causal efficacy. However, although most of the work carried out so far has focused on schizophrenia, aberrant experiences of agency are not restricted to schizophrenic patients. Disturbances of agency can be seen in several other psychiatric and neurological conditions, like obsessive-compulsive behavior (Gentsch et al. 2012), borderline personality disorder (Colle et al. 2020), anosognosia for hemiplegia (Berti et al. 2005), and movement disorders (Moore et al. 2010b, Saito et al. 2017).

Due to the relevance of the results for the main purposes of the present thesis, disturbances of the sense of agency in movement disorders will be described in much detail in the following paragraph.

Disturbances of the sense of agency in movement disorders

Movement disorders are clinical syndromes that cause either an excess of involuntary movement or a paucity of voluntary movements, unrelated to the patient's intention. They include Parkinson's disease, Gilles de la Tourette Syndrome, corticobasal syndrome, and other peculiar conditions, like psychogenic movement disorders. Movement disorders are particularly interesting in the context of agency research for various reasons. For example, it has been discussed that the sense of agency might rely on the functioning of the frontal brain regions, particularly the supplementary and pre-supplementary motor areas (Kühn et al. 2013, Moore et al. 2010a). It follows that the sense of agency might be mapped into the very same sensorimotor system that generates and controls motor execution and is differently compromised in movement disorders. Therefore, it is reasonable to expect that any damage to the sensorimotor system, particularly involving the SMA/pre-SMA network, may affect the subjective experience of agency to various degrees. Moreover, movement disorders might affect the sense of agency generation because of the induced motoric symptoms. For example, the sense of agency might be altered in Tourette's syndrome patients due to the massive occurrence of involuntary movements known as tics. In particular, it has been hypothesized that volitional movements may be hard to distinguish from tics in Tourette's syndrome patients due to the high level of noise in the sensorimotor system induced by the hyperkinetic production (Ganos et al. 2015). Furthermore, disturbances of the sense of agency in movement disorders might be either a consequence of the disease or a side-effect of the disease's pharmacological treatment, as suggested, for instance, for dopaminergic treatment in Parkinson's disease (Moore et al. 2010b). These and other considerations make movement syndromes particularly intriguing from an agency point of view and have motivated the investigation of agency in movement disorders over the years.

Sense of agency disorders in Parkinson's disease have been extensively investigated. For example, Saito et al. (2017) showed that Parkinson's disease patients tend to attribute their action feedback to themselves less often compared to healthy subjects. Moore et al. (2010b) reported that Parkinson's patients on medication show a significant increase in action-effect binding relative to their performance off medication and that of controls. Moreover, Wolpe et al. (2018) showed that the degree of sensory attenuation is negatively related to Parkinson's

disease motor severity but positively related to individual dopamine dose, measured by levodopa dose equivalent.

Disorders of agency in corticobasal syndrome patients have been assessed in a resting-state fMRI study. Wolpe et al. (2014) showed an abnormal binding in patients relative to control subjects, with an increased temporal attraction of the action toward the subsequent tone in the more-affected hand. This increase correlated with the severity of the alien limb and apraxia in that hand. Moreover, differences in binding were related to structural changes in pre-SMA grey matter and functional connectivity at rest between the pre-supplementary motor area and prefrontal cortex (Wolpe et al. 2014).

Growing evidence has shown a major impairment in the sense of agency also in people suffering from psychogenic movement disorders. This impairment is evident in patients' subjective reports (Nahab et al. 2017), as well as in implicit indexes of agency, like intentional binding (Kranick et al. 2013) and sensory attenuation (Pareés et al. 2014) and seems to be specifically linked to the activity of the pre-SMA (Nahab et al. 2017).

Gilles de la Tourette syndrome has become a matter of subject for the agency investigation only recently. Delorme and colleagues (2016) first tested patients' ability to recognize incongruences between their actions and feedback and to make appropriate judgments of agency. They showed that Gilles de la Tourette syndrome patients do not realize that they were not fully responsible for the outcome and, instead, they inflate their judgment of agency (Delorme, Salvador, et al., 2016). However, to date, no investigations have applied implicit approaches for studying the sense of agency in people with Gilles de la Tourette syndrome, leaving the sense of agency investigation in Gilles de la Tourette syndrome incomplete.

For a synopsis of previous studies on the sense of agency in movement disorders, see **Table A3** in the *Appendix.*

Specific aims of this PhD project

The first aim of this PhD (**study one**; chapter two) was to characterize the neurofunctional correlates of the sense of agency in healthy adult participants. As mentioned before, the sense of agency has mainly been studied through explicit experimental paradigms (Farrer et al. 2003, Farrer et al. 2008b). Explicit measures of agency rest upon humans' ability to reflect on their agentic role. They are intuitive, but they are vulnerable to consistent cognitive biases typical of self-report measures (Wegner and Wheatley 1999). Given these limits, it has been recommended that the sense of agency should rather be studied by implicit measures (Haggard 2017). Implicit measures do not imply directly asking people about their agentic role. Instead, they rely on unconscious behavioral biases that provide indirect clues of people's sense of agency. As mentioned, a major one is the intentional binding effect. Whilst it is yet to be fully explicated, the link between intentional binding and the sense of agency is compelling, and the phenomenon has been replicated several times in the literature (Haggard et al. 2002, Moore and Obhi 2012). It follows that coupled with high-resolution neuroimaging techniques, the intentional binding effect represents a powerful tool for exploring the human sense of agency and its neural correlates and gives the impulse to the study of the sense of agency to exceed the limits of previous investigations. The first study in this thesis was specifically designed to explore the neurofunctional correlates of the sense of agency by taking advantage of the intentional binding effect in an fMRI research environment. This first study was an important foundation work needed to better characterize the brain networks underlying the sense of agency that is integral to then understanding how the sense of agency can be described from a functional point of view.

The second aim of this PhD (**study two**; chapter three) was to describe the functional causal role of specific brain regions in the sense of agency generation. To this aim, I modulated the activity of the identified brain network to determine the effect of this modulation on the sense of agency. More precisely, I interfered with the functioning of the agency's brain network by applying repetitive transcranial magnetic stimulation over the local maxima resulting from the fMRI study. I tested the effect of the stimulation in two different time points: at the action planning phase, before the movement execution, and after the actual movement performance, namely at the appearance of the action consequence in the external environment. To this aim, I

tested two independent samples of participants using the same experimental paradigm previously employed in the fMRI study.

The third aim of this PhD (**study three**; chapter four) was to explore the role of the action-outcome in the generation of the sense of agency. In particular, I assessed the experience of agency, and its neural correlates, for action consequences in a different sensory modality compared to that tested in the previous fMRI study. Specifically, while I used visual feedback before, the sensory effect produced by the voluntary action in this task was an auditory tone. I then used an identical experimental paradigm with auditory stimuli, administered to the same sample of participants of study one, in an fMRI setting. I reasoned that this study would provide new insights into possible similarities and differences in both the subjective experience of agency and its neural correlates for diverse action outcomes, allowing me to draw some generalization about the mechanisms of the sense of agency.

The final aim of this PhD (**study four**; chapter five) was to determine whether the sense of agency might be impaired, at the behavioral and/or at the brain activation level, in Gilles de la Tourette Syndrome, a movement disorder characterized by the presence of unwanted movements called tics. I hypothesized that measuring the intentional binding phenomenon might have had the potential of shedding further light on the nature of the Gilles de la Tourette Syndrome, providing, in return, some validity to the inferences formulated on the nature of the sense of agency based on the results on healthy participants. To this aim, I then studied a sample of adult Gilles de la Tourette Syndrome patients by adopting the same experimental paradigm administered to the healthy participants in the same fMRI setting. Thus, I compared the data of the examined Gilles de la Tourette Syndrome patients with the behavioral and fMRI data of the healthy participants.

The experiments described in this thesis have implications for understanding the human sense of agency and provide much-needed empirical evidence regarding its underlying brain correlates. The results also have implications for understanding the aberrant agency experiences in movement disorders, especially regarding Gilles de la Tourette Syndrome. This may open up new opportunities for possible treatments. These topics are discussed in the final chapter of this thesis (chapter six).

Appendix

Table A1 | Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies on sense of agency.

Study						
Authors and year	**Experimental paradigm**	**N**	**Imaging Method**	**Contrast**	**Imaging protocol**	**Main findings**
Farrer & Frith (2002)	Explicit judgment of agency	12	fMRI	Self-attribution vs. external-attribution; external-attribution vs. self-attribution.	Event-related design Whole brain analysis	Self-attribution is associated with activation in the anterior insula. External attribution is associated with activation in the inferior parietal cortex.
Farrer et al. (2003)	Explicit judgment of agency	8	PET	Parametric decrease from self to other visual feedback conditions; Parametric increase self to other visual feedback	Block design Whole brain analysis	Negative correlation between the inferior part of the parietal lobule and the participants' feeling of control. A reverse correlation is observed in the insula.
Leube et al. (2003a)	Explicit judgment of agency	18	fMRI	Positive and negative correlation with the extent of the temporal delay between movement and feedback.	Event-related design Whole brain analysis	Positive correlation between the extent of the temporal delay between movement and feedback and activation of the right posterior superior temporal cortex. A negative correlation is observed in the left putamen.
Leube et al. (2003b)	No measure of agency collected	6	fMRI	Self vs. external perform-observe mismatch; external vs. self-perform-observe mismatch.	Event-related design Whole brain analysis	A right fronto-parietal network is selectively active during the mismatch between one's own observed and performed hand action.
Matsuzawa et al. (2005)	No measure of agency collected	6	fMRI	Synchronous action–effect feedback vs. rest; Asynchronous action–effect feedback vs. rest.	Block design Whole brain analysis	In the synchronous condition, activation in the cerebellum and right parietal lobule is stronger than in the asynchronous condition.
Balslev et al. (2006)	No measure of agency collected	15	fMRI	Asynchronous vs synchronous stimulation.	Event-related design Whole brain analysis	Increased activity in the right temporoparietal cortex in the condition with asynchronous relative to synchronous visual feedback from both active and passive movements.

David et al. (2007)	Explicit judgment of agency	14	fMRI	Congruent vs. incongruent feedback; incongruent vs. congruent feedback.	Block design Regions of interest analysis (on the extra-striate body area)	The extra-striate body area is more active when the visual feedback is incongruent to the subjects' own executed movements.
Schnell et al. (2007)	No direct measure of agency collected	15	fMRI	Visuo-motor congruence vs. visuo-motor incongruence and vice-versa.	Block design Whole brain analysis	Visuomotor incongruence detection is associated with the activity of the rostral inferior parietal lobule.
Farrer et al. (2008b)	No direct measure of agency collected	15	fMRI	Perturbed visual feedback vs unperturbed visual feedback.	Block design Regions of interest analysis (left and right angular gyri).	Angular gyrus activity is associated with both awareness of discrepancy between intended and movement consequences and awareness of action authorship.
Kontaris et al. (2009)	No direct measure of agency collected	11	fMRI	Visuo-motor congruence vs. visuo-motor incongruence and vice-versa.	Block design Regions of interest analysis (extra-striate body area and fusiform body area)	Stronger activation of the posterior-superior Temporal Sulcus in the incongruent condition than in the congruent condition.
Spengler et al. (2009)	Explicit judgment of agency	18	fMRI	Parametric increase with increasing/decreasing discrepancy of action-effect congruency.	Block design Whole brain analysis	The activity in the temporo-parietal junction increases with the increasing discrepancy of action-effect congruency
Yomogida et al. (2010)	No direct measure of agency collected	24	fMRI	Agency violation vs. sensory match violation.	Event-related design Whole brain analysis	Agency-error-specific activation was observed in the supplementary motor area, left cerebellum, right posterior parietal cortex, and right extrastriate body area.
Nahab et al. (2011)	Explicit judgment of agency	20	fMRI	Parametric increase with to the loss of sense of agency	Block design Whole brain analysis	They identified 2 discrete networks: the leading and lagging networks. The leading network has the role of mismatch detection; the lagging network receiving this information and mediating its elevation to conscious awareness.
Tsakiris et al. (2010)	No direct measure of agency collected explicit	19	fMRI	Active Synchronous – Passive Synchronous) exclusively masked by (Active Asynchronous – Passive Asynchronous	Block design Whole brain analysis	Activity in the right superior parietal cortex, the pre-supplementary motor area, the dorsal premotor cortex bilaterally, and the cerebellum bilaterally. pre-SMA is linked to the sense of agency and absent in the body-ownership condition. No shared activations that would support the additive model are found.

Chambon et al. (2013)	Explicit judgment of agency	22	fMRI	Compatible action priming condition vs. not compatible action priming.	Event-related design Whole brain analysis	Greater activity in the left and right dorsolateral prefrontal cortices and left putamen for compatible trials relative to incompatible trials.
Fukushima et al. (2013)	Explicit judgment of agency	17	fMRI	Self-attribution vs. external attribution.	Event-related design Whole brain analysis	Self-attribution is associated with activity in posterior midline areas, including the precuneus and posterior cingulate cortex.
Kuhn et al. (2013)	Implicit (intentional binding measure)	17	fMRI	Active movement condition vs passive movement condition, both parametrically modulated with the intentional binding effect.	Event-related design Small Volume Correction on ROIs (SMA, angular gyrus, insula, superior frontal medial cortex and precuneus).	SMA proper is more strongly associated with the perceived action-tone interval than with perception of a control interval following a passive movement.
Renes et al. (2015)	Explicit judgment of agency	23	fMRI	Self-attribution vs. external attribution.	Event-related design Whole brain analysis	Self-attribution is associated with increased activation in the inferior parietal lobule, the superior frontal cortex and the medial prefrontal cortex.
De Bézenac et al. (2016)	No measure of agency collected	24	fMRI	Conditions characterized by self-produced feedback and feedback produced by others.	Block design Whole brain analysis	Brain regions related to motor cognition show a quadratic response to the self-to-other manipulation.

Table A2 | Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) studies.

Study					
Authors and year	**Experimental paradigm**	**N**	**Experimental Task**	**Stimulation details**	**Main findings**
MacDonald et al. (2003)	Explicit judgment of agency	12	Action-recognition tasks.	Low-frequency rTMS (0.6 Hz) for 15 minutes, before the execution of the task. Stimulation site: left superior parietal lobule (SPL); control site: left temporal cortex.	Following the SPL stimulation, participants' assessments of asynchrony are impaired for active but not passive movements. No significant changes are observed after rTMS applied over the control site.
Preston et al. (2008)	Explicit judgment of agency	10	Action-recognition tasks.	Single pulse TMS during the task. Stimulation site: right inferior parietal lobe (rIPL); control site: vertex.	When TMS is applied over rIPL, participants are more likely to misattribute agency to the computer.
Moore et al. (2010a)	Implicit (intentional binding)	10	Temporal judgment task.	Theta-burst stimulation (three pulses at 50Hz repeated at 200 ms intervals) before the task execution. Stimulation site: pre-SMA; control site: sensorimotor hand area and the sensorimotor leg area.	Disruption of the pre-SMA reduces the temporal linkage between a voluntary key-press action and a subsequent electrocutaneous stimulus. Disruption of the sensorimotor cortex has no significant effect.
Ritterband-Rosenbaum et al. (2014)	Explicit judgment of agency	14	Action-recognition tasks.	rTMS (1s trains of 10 Hz), during the execution of the task. Stimulation site: inferior parietal cortex (IPC); control site: vertex.	Following IPC stimulation subjects are more likely to experience self-controlled movements as being externally perturbed compared to the control site and the stimulation-free control.
Weiss et al. (2014)	Explicit judgment of agency	29	Action-recognition tasks.	Single pulse TMS during the task. Stimulation site: left motor cortex Timing: after observing/performing the movement.	Corticospinal excitability varies with the degree of temporal correspondence of the executed and observed movements. Moreover, explicit agency judgments can be predicted from corticospinal excitability.
Chambon et al. (2015)	Explicit judgment of agency	12	Compatible action priming condition and not compatible action priming conditions.	Single-pulse TMS during the execution of the task. Stimulation sites: inferior parietal cortex (IPC) & dorsolateral prefrontal cortex; control site: none.	TMS over left IPC at the time of action selection disrupts perceived control over subsequent effects of action.

Khalighinejad & Haggard (2015)	Implicit (intentional binding)	55	Temporal judgment task.	tDCS, 1 mA for 25 min before the task execution. Stimulation site: dorso-lateral prefrontal cortex (DLPFC) and angular gyrus (AG).	IB is diminished by anodal stimulation of the left parietal cortex and, to a lesser extent, by stimulation targeting the left DLPFC. Cathodal AG stimulation has no effect.
Cavazzana et al. (2015)	Implicit (intentional binding)	15	Participants observed a stream of unpredictable consonants at the center of a screen to detect the letter displayed when a given event of interest (i.e., a voluntary action or a sound) occurred.	tDCS. A constant current (1.5 mA) was applied for 20 min in the active stimulation conditions. Stimulation site: pre-SMA. Control site: auditory cortex	Sham stimulation significantly differs from anodal and cathodal stimulations, which both tend to reduce IB producing an inhibitory effect when applied over pre-SMA.
Hughes et al. (2018)	Explicit & Implicit	63	Temporal judgment task and explicit judgments of agency.	tDCS, 1 mA for 20 min before the task execution. Stimulation site: left and right Temporal parietal junction (TPJ).	The modulation of explicit agency ratings by action-outcome congruency is significantly reduced by right TPJ stimulation but not left TPJ stimulation. Implicit agency is not affected in either stimulation condition.

Table A3 | Previous studies on the sense of agency in movement disorders.

Study			
Author and year	**Participants**	**Task**	**Main findings**
Parkinson's disease(PD)			
J.W. Moore et al. (2010b)	9 PD patients and 9 healthy controls (HC).	Temporal judgment task (Intentional binding measure). Patients completed two testing sessions (off and on) on the same day.	PD patients off medication showed no significant change in action-effect binding relative to controls. PD patients on medication showed a significant increase in action-effect binding relative to their own performance off medication.
L. Ricciardi et al. (2017)	19 PD patients with ICB (PD-with impulsive compulsive behaviors), 19 PD-no-ICB and 19 healthy controls (HC).	Temporal judgment task (Intentional binding measure).	PD-ICB had significantly stronger action binding than HC and PD-no-ICB. There was no difference between PD-no-ICB and HC.
N. Saito et al. (2017)	9 PD patients on medication and 25 healthy controls (HC).	Task 1: Action recognition task. Task 2: Temporal judgment task (Intentional binding measure).	PD patients showed less attribution of the given feedback to themselves compared to the HC group. Actions were not experienced as having shifted towards their effects in the patient group. Tone binding did not differ between PD and HC.
N. Wolpe et al. (2018)	18 Patients with idiopathic PD on medication and 175 healthy controls (HC).	Force matching task (sensory attenuation measure).	Overall sensory attenuation did not differ between medicated PD patients and HC. The degree of attenuation was negatively related to PD motor severity but positively related to individual patient dopamine dose, as measured by levodopa dose equivalent.
Gilles de la Tourette syndrome(GTS)			
C. Delorme et al. (2016b)	37 GTS patients and 19 healthy subjects. Among the GTS patients, 19 were unmedicated and 18 were treated with antipsychotics.	Action task requiring explicit judgments. The task included several conditions, where the objective control over the cursor could be normal, disrupted or artificially enhanced.	GTS patients, independently of medication status, had an illusion of agency in the task condition where their performance was artificially enhanced. The propensity to illusions of agency was negatively correlated with global disease severity.

Corticobasal syndrome			
N. Wolpe et al. (2014)	10 patients meeting clinical diagnostic criteria for corticobasal syndrome (CBS) and 16 healthy subjects.	Temporal judgment task (Intentional binding measure) in an fMRI setting.	CBS patients showed increased action binding. Behavioral variability was related to changes in grey matter volume in pre-SMA. Changes in functional connectivity at rest between the pre-SMA and prefrontal cortex were proportional to changes in binding.
Psychogenic/functional movement disorders(P/FMD)			
S.M. Kranick et al. (2013)	20 patients with motor conversion disorder	Intentional binding task executed after participants completed conditioning blocks in which high, medium, and low tones were coupled to images of happy, fearful, and neutral faces.	Patients had reduced overall binding scores relative to healthy volunteers, suggesting a reduced sense of agency. There was no effect of the emotional stimuli (faces) or other interaction effects.
I. Pareés et al. (2014)	14 PMD patients and 14 HC.	Force matching task (sensory attenuation measure).	HC consistently overestimated the force required when pressing directly on their own finger than when operating a robot. PMD patients did not, indicating a significant loss of sensory attenuation.
C. Delorme et al. (2016a)	20 cervical dystonia patients and 20 healthy controls (HC).	The task included several conditions in which the control over the cursor could be disrupted by adding a spatial or a temporal discrepancy between the mouse and the cursor's movements. Participants had to acknowledge these discrepancies and reflect them in metacognitive judgments of agency.	Cervical dystonia patients did not fully recognize alterations of agency when a temporal lag was added between their movement and the visual feedback. They relied predominantly on their perceived performance to provide judgments of agency and less on their objective degree of controls.
A. Marotta et al. (2017)	21 Patients with PMD and 21 HC.	Moving Rubber Hand Illusion (mRHI), in which passive and active movements can differentially elicit agency, ownership or both. Explicit measures of agency and ownership were obtained via a questionnaire.	Patients and controls showed a similar pattern of response: when the rubber hand was in a plausible posture, active movements elicited strong agency and ownership; implausible posture of the rubber hand abolished ownership but not agency; passive movements suppressed agency but not ownership.
F. Nahab et al. (2017)	21 patients with PMD and 20 HC.	Virtual-reality movement paradigm in an fMRI setting. Participants observed a computer screen that displayed a moving hand that mimicked their movements completely (100% control), was completely random (0% control), or was an intermediate mixture (25%, 50% or 75% control).	Individuals with PMD experience the tendency to overestimate control over the virtual hand. Moreover, they lacked the ability to recognize the loss in control. Selective dysfunction of the SA neural network, whereby the dorsolateral prefrontal cortex and pre-supplementary motor area on the right did not respond differentially to the loss of movement control.

Chapter 2

Study one: Investigating the neurofunctional correlates of the sense of agency using the intentional binding effect[1]

Introduction

The ability to change the external world through our own voluntary actions is a central aspect of human experience. Typically, this experience also produces a peculiar feeling of controlling external events, called the "sense of agency" (Haggard 2017). Although extensively investigated, both the subjective experience of agency and its neurobiological correlates remain poorly understood. One major limit in the previous literature consists of the methodological problem of designing experimental paradigms able to capture this elusive feeling of control that accompanies and characterizes voluntary actions in an ecologically relevant state while in a

[1] This chapter contains experiments already published in:
Zapparoli, L.*, S. Seghezzi*, E. Zirone, G. Guidali, M. Tettamanti, G. Banfi, N. Bolognini & E. Paulesu (2020b) How the effects of actions become our own. *Sci Adv,* 6.

* shared first authorship

research environment. Several studies have sought to identify the brain network that underlies the sense of agency through explicit agency-attribution judgments. Most of these studies used action recognition tasks, in which spatial or temporal distortion was added between participants' movements and the provided visual feedback. They consistently showed activations of the inferior parietal cortex and the angular gyrus in conditions in which visual feedback was judged as no-self-generated, unrelated to participants' intention ("External agency" condition, see for example Farrer and Frith 2002, Farrer et al. 2003, Farrer et al. 2008b). In contrast, previous neuroimaging studies generally failed to identify any clear neural correlates for the self-judgments of agency, i.e., conditions in which feedback was judged as self-generated ("Self-agency condition"). The only area consistently associated with the self-agency attribution was the posterior insula (see for example, Farrer and Frith 2002). However, the role of the insula in the genesis of the sense of agency is still unclear, and it is likely to be associated with a general multisensory integration processing of the incoming stimuli (Kurth et al. 2010b, Cauda et al. 2011). Moreover, explicit judgments of agency are rare in everyday life. While they might be significant in social settings where individuals may be held responsible or liable for the consequences of their behavior, the everyday experience of agency mostly relies on the implicit background feelings of being in control (Kühn et al. 2013). Indeed, humans constantly feel a flow between the actions they intend to perform and their external effects (a "feeling of agency", Synofzik et al. 2008a). Given these limits, it has been recommended that the sense of agency should be studied by implicit measures, instead (Haggard 2017). A major one is the intentional binding effect (Haggard et al. 2002, Moore and Obhi 2012). It has been shown that when individuals make a voluntary action to cause a sensory effect a short time later, they perceive the time interval between the action and the effect as shorter than the same time interval following a passively-induced movement (Haggard et al. 2002). This temporal distortion pattern has thus led to the suggestion that this effect could form a useful implicit marker of the sense of agency. Thus, since its seminal introduction (Haggard et al. 2002), this bias in the perceived time of voluntary actions and their outcomes has become one of the most widely used implicit markers of the sense of agency.

To date, only one study took advantage of this putative measure of the sense of agency to explore the subjective experience of agency and its neurobiological correlates. In particular, Kühn et al. (2013) showed the supplementary motor area (SMA) proper was more strongly associated with the time compression following a voluntary action than with the perception of

a control interval following a passive movement (Kühn et al. 2013). This study provides the first evidence of a significant association between the SMA and the intentional binding effect. However, this study was restricted to test the specific contribution of the SMA and the angular gyrus to the sense of agency. Consequently, it could not draw strong anatomical conclusions about the precise location of the neural correlates of the sense of agency.

In this study, I aimed at identifying the brain regions associated with the sense of agency, taking advantage of the intentional binding effect as a proxy for the sense of agency. To this aim, I used the perceived compression between the time of actions and their effects as a putative marker of the self-agency experience in a new whole-brain functional magnetic resonance imaging (fMRI) study.

I designed a temporal judgment task in which participants estimated the time interval between a button press and a subsequent visual event that could follow the action by 200, 400, or 600ms of delay. Since many factors influence time perception, shifts in time perception cannot be considered diagnostic of a sense of agency without an appropriately chosen control condition (Haggard 2017). Therefore, while in one condition, the feedback was elicited by the participant's active movement, in another condition, it was generated by a passive movement. I reasoned that a difference in intentional binding between these conditions could reliably be interpreted as a difference in the sense of agency.

In line with the literature on the intentional binding effect (Haggard et al. 2002, Moore and Obhi 2012), I hypothesized that participants underestimate the time interval between actions and effects in the active condition compared to the passive condition. Furthermore, I anticipated the magnitude of the intentional binding effect in the active condition to differ based on the specific features of the trial, namely the temporal proximity of the action and the outcome. The role of temporal contiguity in the self-agency experience is still unclear. Temporal contiguity represents a strong cue to infer causality, i.e., the causal relationship between an action and an external event. However, while Haggard et al. (2002) found a stronger intentional binding at 250ms of delay (Haggard et al. 2002), Kuhn et al. (2013) described an effect at 400ms of delay (Kühn et al. 2013), and Buehner and Humphreys (2009) found that intentional binding was preserved at delays of up to 1300ms (Buehner and Humphreys 2009). Thus, it remains to be established to what extent actions and feedback should be tied in time for the arising of a sense of agency.

Finally, I hypothesized that the activity of some brain regions within the frontoparietal network correlates with the perceived compression. In particular, in line with the previous neuroimaging and non-invasive brain stimulation literature, I expected significant activations of the SMA (Kühn et al. 2013) and the parietal cortex (Farrer and Frith 2002, Farrer et al. 2003, Farrer et al. 2008b, Preston and Newport 2008, Ritterband-Rosenbaum et al. 2014, van Kemenade et al. 2017) associated with the strength of the effect.

This experiment represents an important foundation study needed to better characterize the subjective experience of agency and its neurobiological bases and represents the prerequisite to then explore the sense of agency system from a functional point of view.

Methods

Participants

Twenty-five healthy adult subjects (mean age: 25.7 ± 3.8 years; mean education: 15.6 ± 2.5 years; male/female: 12/13) with no history of psychiatric or neurological diseases participated in this study. One participant was eliminated from the fMRI analysis due to strong movement artifacts. The resulting 24 participants (mean age: 25.4 ± 3.5 years; mean education 15.5 ± 2.5 years; male/female: 11/13) were all right-handed as assessed by the Edinburgh handedness inventory (Oldfield 1971).

Before the experiment, each subject completed a brief neuropsychological screening. The neuropsychological battery included the Mini-Mental State Examination (MMSE, Folstein, Folstein and McHugh 1975), the Raven's Colored Progressive Matrices (Raven's Matrices, Raven, Raven and Court 1998) and the Frontal Assessment Battery (FAB, Dubois et al. 2000). No subject reported pathological scores at any test.

The study protocol was approved by the local Ethics Committee (IRCCS *San Raffaele* of Milan; Prot. SOA, 149/INT/2016). Informed written consent was obtained from all subjects according to the Helsinki Declaration (1964). All subjects participated in the study after the nature of the procedure had been fully explained.

Procedure

The experiment was performed in a single session in one day.
fMRI scans were acquired during the execution of a behavioral task. The task had an event-related interleaved structure. It lasted approximately twelve minutes, depending on the individuals' reaction times.
Stimuli presentation was controlled by Cogent 2000 MATLAB Toolbox (MathWorks). Visual stimuli were presented using VisuaStim fiber-optic goggles (600x800 pixel resolution). Responses were recorded through response boxes placed under the participant's hands (Resonance Technology Inc., Northridge, CA, USA).
Before the experiment, subjects performed a training session made of 10 trials, when they received feedback on their performance.

Experimental task

Participants performed a temporal judgment task, which consisted of active and passive trials. Each trial started with the presentation of the picture of a turned-off lightbulb on the screen. For the active trials, the base of the bulb was colored in green. For the passive trials, the base was colored in red. Participants were instructed to press a button with their right index finger every time they saw a green lightbulb (active trials). They were invited to make the press at their own time. This was done to elicit a well-prepared, self-initiated button press, rather than an automatic movement as a reflex to the instruction. They were instructed to refrain from acting when the base of the lamp was colored in red (passive trials). In this case, the experimenter present inside the MRI room pressed participants' right index finger to induce a passive movement. In both conditions, the button press caused the illumination of the lamp. This could happen after 200, 400, or 600 milliseconds (ms) of delay. The feedback lasted 500ms. After 2000ms, participants judged the perceived time interval between the button press and the illumination of the lamp. Judgments were reported by means of a visual scale at which they responded using a five-key response keypad placed under their left hand. They used their fingers to select one of five possible response options: 1ms, 200ms, 400ms, 600ms, and 800ms. The lowest and the highest response options were included to make it possible for the participants to underestimate and overestimate each presented time interval.

The task consisted of 60 trials, equally distributed between active and passive conditions, with ten trials for each delay. The inter-stimulus interval randomly varied between 1500ms and 2500ms. For a graphical representation of the task, see **Figure 1**.

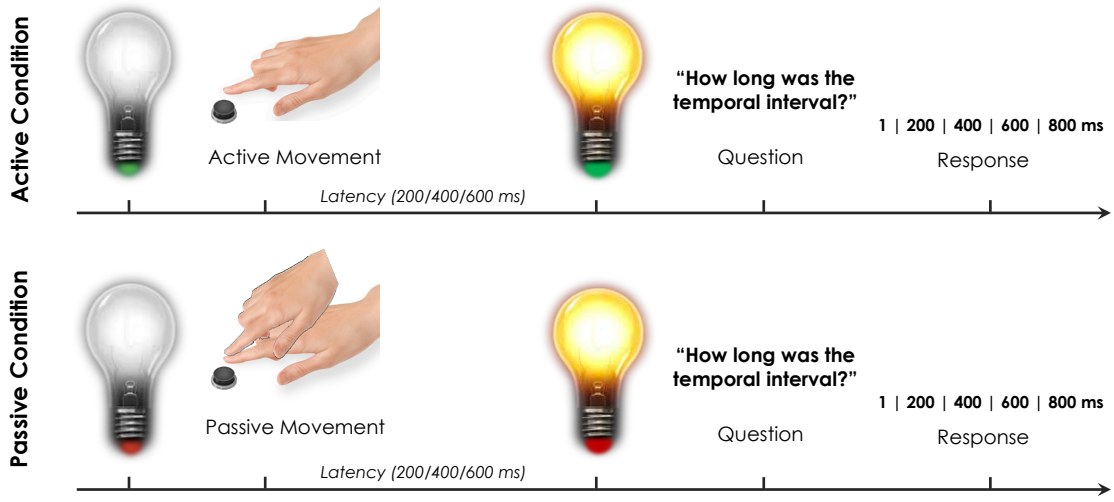


Figure 1 | Experimental task. Graphical illustration of an experimental trial for active and passive conditions. During the active trials, participants pressed a button with their right index finger at their own time after the presentation of the cue. In the passive trials, participants were instructed to stay still while an experimenter pressed their finger to produce a passive movement. In both conditions, the button press caused an action-consequence: the lightening of a lamp. The consequence was presented after a variable delay of 200, 400, or 600ms. Participants then judged the perceived time interval between their button press and the action-consequence.

Statistical analyses of the behavioral data

Behavioral data collected during the fMRI experiment were analyzed using the software SAS (Statistical Analysis System, version 9.4).

In line with the description of the intentional binding phenomenon (Haggard et al. 2002), the time compression represented the indirect measure of the sense of agency and was entered into the model as the dependent variable. It refers to the difference between the estimated and the real duration of the action-outcome delay. More negative time compression values stood for stronger degrees of the perceived sense of agency.

$$Time\ Compression = Estimated\ delay - Actual\ delay$$

The independent variables of the model were the factors "Condition" (active/passive) and "Delay" (200/400/600ms). The model was tested by using linear mixed models with random intercept. Significant interactions were further explored by means of planned Bonferroni corrected post-hoc comparisons.
Before applying linear mixed models, data distribution was inspected using the skewness-kurtosis graph of Cullen and Frey (Cullen and Frey 1999), which provides the best fit for an unknown distribution according to skewness level and kurtosis. The present data had a distribution that conforms to the normal distribution.

fMRI data acquisition and analysis

MRI scans were acquired using a 1.5 T Siemens *Avanto* scanner, equipped with gradient-echo echo-planar imaging (flip angle 90°, TE=40ms, TR=2000ms, FOV=250 mm, matrix=64x64). The overall number of the collected fMRI volumes varied from 269 to 292 volumes depending on the individual reaction's times. The first 15 volumes of the block corresponded to the instructions' presentation and were discarded from the analyses.

Pre-processing

After the image reconstruction, raw data were visualized and converted from DICOM to the NIFTI format were performed by means of the MRIcron (www.mricro.com) software. All the subsequent data analyses were executed in MATLAB R2014a (Mathworks Natick MA USA) using the software Statistical Parametric Mapping (SPM12, Wellcome Department of Imaging Neuroscience, London, UK).
fMRI scans were realigned to the first image of the run to account for any head movement during the experiment. The structural T1 image was coregistered to the functional mean image to allow a more precise normalization. Then, the unified segmentation and nonlinear warping approach of SPM12 was applied to normalize structural and functional images to the MNI (Montreal Neurological Institute) template to permit group analyses of the data (Ashburner and Friston 1999, Friston et al. 1995). The data matrix was interpolated to produce 2 x 2 x 2 mm voxels. The stereotactically normalized scans were finally smoothed using a Gaussian filter of 10 x 10 x 10 mm to improve the signal-to-noise ratio and make the data suited for cluster-level correction for multiple comparisons (Flandin and Friston 2017).

The BOLD signal associated with each experimental condition was analyzed by a convolution with a canonical hemodynamic response function (HRF) (Worsley and Friston 1995). Global differences in the fMRI signal were removed from all voxels with proportional scaling. High-pass filtering (128s) was used to remove artefactual contributions to the fMRI signal.

First level fixed-effect analyses

A fixed-effect block-design analysis was performed for each subject to characterize the BOLD response associated with the task.

In particular, the brain activity between the appearance of the instruction (the green or red turned-off lightbulb) and the action consequence (the illumination of the lamp) was separately specified for each condition (active and passive conditions) and each action-outcome delay (200/400/600ms), for a total of six regressors.

The brain activity occurring between the appearance of the evaluation scale and the response was similarly specified, separately for each condition and delay (for a total of six regressors) and added to the statistical model as non-interest regressors. In addition, the parameters obtained from the realignment procedure were added to the model to partial out the effect of motion artifacts on the estimates of the beta parameters.

For each subject for each action-outcome delay, I then generated a contrast image of the comparison Active condition > Passive condition, for a total of three contrast images per participant.

Second level random effect analysis

The contrast images (Active condition > Passive condition, for each action-outcome delay) were entered in separate second-level analyses, conforming to a random-effect approach (Holmes and Friston 1998).

One-way ANOVA analysis

I first performed an explorative one-way ANOVA analysis to test the effect of the comparison Active condition > Passive conditions - irrespective of the different action-outcome delays - and the interaction effect between the factor “Condition” (active/passive) and the factor “Delay” (200/400/600ms). This model consisted of three regressors of interest, one for each

condition and delay (Active condition > Passive conditions at 200ms, Active condition > Passive conditions at 400ms, Active condition > Passive conditions at 600ms).

Linear regression analyses

I then performed three separate linear regression analyses, one for each action-outcome delay, to test the hypothesis that the activity of some brain regions covaried with the individually measured intentional binding effect at specific time-windows.

Crucially, since the contrast images used in this analysis contained the differential effect between active and passive trials (Active condition > Passive conditions, at the specific action-outcome delay), differential time compression values between active and passive trials (mean time compression in the Active condition – mean time compression in the Passive conditions, at the specific action-outcome delay) were used as a regressor here.

All the results reported survive a correction for multiple comparisons: I used the nested-taxonomy strategy recommended by Friston et al. (Friston et al. 1996), including regional effects meeting either a cluster-wise or voxel-wise FWER correction. The voxel-wise threshold applied to the statistical maps before the cluster-wise correction was $p<0.001$ uncorrected, as recommended by Flandin and Friston (Flandin and Friston 2017). For clusters significant at the $p<0.05$ FWER-corrected level, I also report the other peaks at $p<0.001$.

Results

Behavioral Results

I found a significant effect of the factor "Delay" ($F_{(2,48)}$=4.45; p=0.017) and a significant "Condition*Delay" interaction ($F_{(2,1297)}$=6.8; p=0.001). The factor "Condition" was not significant ($F_{(1,24)}$=3.47; p=0.075).

The Condition*Delay interaction was further explored with planned post-hoc comparisons. The results showed that time compression was significantly stronger in the active than passive conditions at 200ms of delay. There was no difference between active and passive conditions at longer delays. For more details, please see **Table 1** and **Figure 2**.

Table 1 | Planned post-hoc comparisons. Comparisons between time compression values in the active and passive conditions at different action-outcome delays. For each comparison, I reported the mean difference, the standard error (SE), the value of the statistic, the corresponding degrees of freedom (df), and the associated Bonferroni-corrected p-value. Asterisks indicate significant results at $p < 0.05$ Bonferroni corrected.

Comparison									
Condition	**Delay**		**Condition**	**Delay**	**Difference**	**SE**	**test**	**df**	**Bonferroni-corrected p**
Passive	200	-	Active	200	64.36	19.3	3.34	1297	0.003*
Passive	400	-	Active	400	31.85	19.1	1.67	1297	0.288
Passive	600	-	Active	600	-17.45	10.0	-0.92	1297	p>0.99

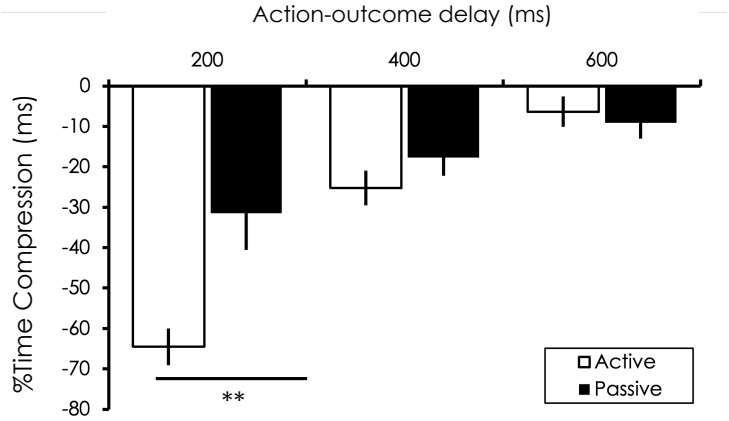


Figure 2 | Behavioural results showing the intentional binding effect at 200ms action-outcome delay. Error bars = standard error; asterisks indicate significant results at $p < 0.05$ Bonferroni corrected. Please note that the results are reported here as a percentage of the compression with respect to the action-outcome delay (for visualization only).

fMRI results

One-way ANOVA analysis

Active condition > Passive condition

The comparison between active and passive conditions showed significant activation of the motor and premotor network, including the bilateral middle cingulum, the pre- and the supplementary motor area, the left precentral gyrus, and the cerebellum bilaterally. For more details, please see **Table A1** and **Figure A1** in *Appendix*.

Passive condition > Active condition

No region displayed a significant effect. As one would expect given the effect of touches to the right hand in the passive condition, there was a sizeable trend in the left secondary somatosensory area (X= -44; Y= -24; Z= 18; *Z* score=3.4).

Interaction effect between the factor Condition and the factor Delay

No region displayed a significant effect.

Linear regression analyses

Linear regression analysis for the differential time compression values (active > passive trials) at 200ms action-outcome delay.

The results showed a significant correlation between the differential time compression values of individual participants (mean time compression in the Active condition – mean time compression in the Passive conditions at 200ms) and the BOLD signal (Active condition > Passive conditions at the 200ms) in a wide brain network including the bilateral insular cortex extending to the left superior temporal pole, the bilateral precuneus and cerebellum, the left pre-SMA, the left hippocampus, the right superior frontal gyrus (Brodmann areas 6 and 9), and the right inferior parietal lobule (Brodmann area 40) extending to the right postcentral gyrus (Brodmann areas 3,2). See **Table 2** and **Figure 3**.

Linear regression analysis with the differential time compression values (active > passive trials) at 400 and 600ms action-outcome delays.

No region displayed a significant correlation with the differential time compression values at 400 and 600ms of delays between action and the outcome.

Table 2 | Linear regression analysis between the fMRI data (Active condition > Passive conditions at the 200ms) and the differential time compression individual values (mean time compression in the Active condition – mean time compression in the Passive conditions at 200ms). °p<0.05 FWER corrected (cluster level).

Brain regions (BA)	MNI coordinates											
	Left hemisphere						Right hemisphere					
	x	y	z	Z-score	P-value	Cluster size	x	y	z	Z-score	P-value	Cluster size
Superior Frontal Gyrus (6/9)	--	--	--	--	--	--	20	30	50	4.23°	p<0.0001	174
	--	--	--	--	--	--	10	40	46	3.9°	p<0.0001	
Pre-SMA (6)	-16	12	64	4.00°	p<0.0001	158	--	--	--	--	--	--
	-10	16	62	3.78°	p<0.0001		--	--	--	--	--	--
	-6	18	62	3.46°	0.0003		--	--	--	--	--	--
Insula	-38	12	0	3.8°	p<0.0001	254	44	16	-6	4.32°	p<0.0001	243
	-46	8	0	3.29°	0.0005		--	--	--	--	--	--
	-42	6	-12	4.09°	p<0.0001		--	--	--	--	--	--
	-42	6	-4	3.78°	p<0.0001		--	--	--	--	--	--
Postcentral Gyrus (3)	--	--	--	--	--	--	52	-26	48	3.55°	0.0002	331
Inferior Parietal Lobule (40) / Postcentral Gyrus (2)	--	--	--	--	--	--	36	-40	66	4.03°	p<0.0001	331
	--	--	--	--	--	--	40	-38	62	3.93°	p<0.0001	
	--	--	--	--	--	--	52	-30	50	3.59°	0.0002	
Precuneus (7)	-2	-60	52	3.44°	0.0003	204	10	-62	62	3.96°	p<0.0001	204
	--	--	--	--	--	--	0	-60	48	3.38°	0.0004	
	--	--	--	--	--	--	14	-68	60	3.47°	0.0003	
	--	--	--	--	--	--	0	-58	58	3.51°	0.0002	
Superior Temporal Pole (38)	-44	10	-18	4.33°	p<0.0001	254	--	--	--	--	--	--
Hippocampus (27)	-20	-30	0	4.35°	p<0.0001	679	--	--	--	--	--	--
	-20	-34	-2	3.70°	0.0001							
Parahippocampal gyrus (27)	-18	-34	-6	3.58°	0.0002	679	18	-36	-10	4.12°	p<0.0001	679
Cerebellum_4_5	-6	-42	-12	3.53°	0.0002	679	10	-44	-10	4.23°	p<0.0001	
	-14	-36	-10	3.97°	p<0.0001		8	-48	-2	3.6°	0.0002	

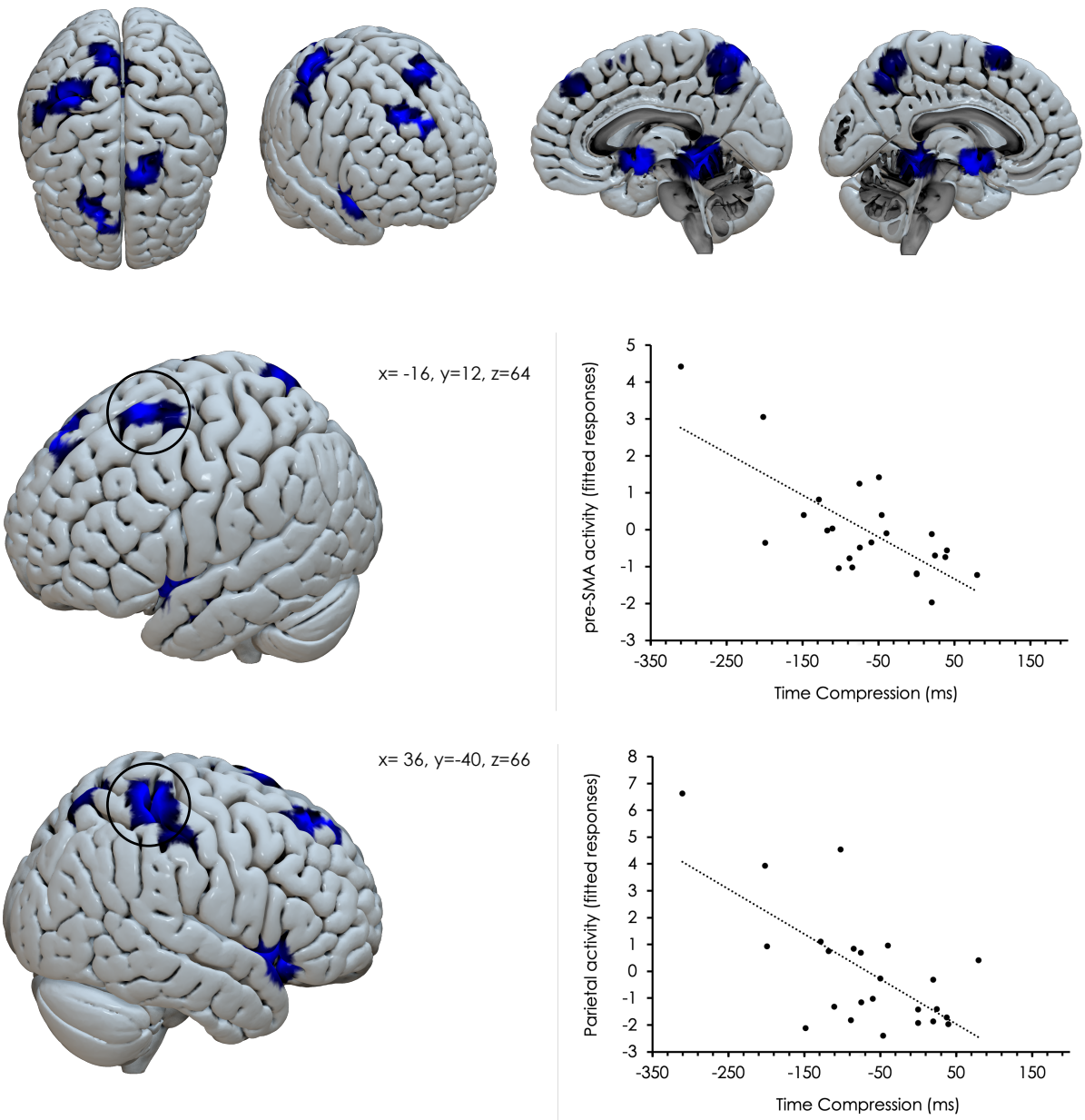


Figure 3 | fMRI results showing brain regions which activity displayed a significant association with the magnitude of the intentional binding effect at 200ms of delay. Below, the plot of the regression analysis between the individual differential time compression values and the brain activity (fitted responses) in the left premotor (pre-SMA) and right parietal local maxima.

Discussion

The present study investigated the neural correlates of a distortion in time perception following voluntary action, which is taken as a putative implicit marker of the sense of agency. This distortion in time perception is called "intentional binding" (Haggard et al. 2002) and refers to a perceived compression between the time of voluntary action and the time of the following sensory effect.

I measured this intentional binding effect through a temporal judgment task in which participants estimated the time interval between a button press and a subsequent visual event that followed the action by 200, 400, or 600ms of delay. As mentioned, since many factors influence time perception, shifts in time perception cannot be considered diagnostic of a sense of agency without an appropriately chosen control condition (Haggard 2017). Therefore, while in one condition, the feedback was elicited by the participant's active movement, in another condition, it was generated by a passive movement. Any difference in the intentional binding between these conditions was then interpreted as a difference in the sense of agency, and the associated changes in the brain activity as neural correlates of the self-agency experience.

Behavioral results

Behavioral results replicate the findings of previous studies (Haggard et al. 2002, for a review, see Moore and Obhi 2012), showing shorter interval estimations in the active condition compared to the passive condition. However, this difference was strongly different based on the time delay between the action and its sensory effect: while I observed a significant intentional binding effect at 200ms of delay, the same effect was greatly reduced at 400ms and absent at 600ms.

To date, the role of contiguity (i.e., the temporal proximity of the action and the effect) in the sense of agency is still unclear. At first sight, the present results seem to suggest that the closer together in time these events are, the stronger the sense of agency. These data are also in line with previous studies showing that the intentional binding effect is stronger for shorter action-outcome delays. For example, in their seminal study, Haggard et al. (2002) explored the intentional binding effect at action-outcome delays of 250, 450, and 650ms and found that the temporal linkage between the action and the effect was weaker at longer delays (Haggard et al.

2002). However, there are a plethora of other studies showing the putative intentional binding effect at longer delays. For example, Kuhn et al. (2013) described a significant difference at 400ms of delay, while the same effect was not significant at 200 and 300ms (Kühn et al. 2013). Buehner and Humphreys (2009) found an intentional binding effect even at action-outcome delays of 1300ms (Buehner and Humphreys 2009). It is then likely that other factors than the mere contiguity may drive the sense of agency and justify the plurality of its manifestations. Among these, high-level causal beliefs and expectations may play a crucial role in real-life situations, in which the action-outcome association is not trivial. In those situations, precise expectations about the outcome could derive from prior experiences with the specific action-outcome associations. These expectations may then have a role in determining the particular time window for the sense of agency to occur, tuned to time intervals that mimic the previous experience for a given action and its usual effects. Crucially, one should consider that, unlike other studies (Buehner and Humphreys 2009, Haggard et al. 2002, Kühn et al. 2013), the stimuli adopted in the present experiment had a clear link to real-life situations. Precisely, they mimicked the context of switching on the light, a simple action that individuals repeat many times a day. Remarkably, a latency of about 200ms is the one that can be measured in real life between the time when the agent press an electricity light-switch and the time that a conventional light bulb takes to be fully on (Sivak et al. 1994). An intentional binding effect at 200ms of action-outcome delay is thus in line with the suggestion that the sense of agency may emerge for action consequences that happen at action-outcome delays that are compatible with the expectations we made based upon our previous experiences. At the same time, we may not experience a sense of agency for action consequences that happen unexpectedly.

This hypothesis opens the way to further studies to explore the effect of different outcome expectations on the sense of agency. It also begs the question about the possibility of manipulating these previous expectations to intervene on the individuals' sense of agency, with new options for treatment disturbances of the agency (for a deeper discussion about this point, please see the general discussion, chapter six).

Neurofunctional results

I then focused on the brain activity that accompanies the sense of agency. Precisely, I explored the brain regions whose activity shows a significant correlation with the individually measured intentional binding effect at different action-outcome delays.

The results showed that the intentional binding effect was mirrored by meaningful brain activity in a broad network, including the bilateral insular cortex, precuneus and cerebellum, the left pre-SMA, the left hippocampus, the right superior frontal gyrus, and the right inferior parietal lobule. Importantly, the relationship between the intentional binding and the activity of this brain network was significant only at 200ms of delay, when there was a sizeable difference in the perceived time compression between the active and passive conditions. No significant effects have been found at 200 and 600ms.

This evidence provides validation of the behavioral findings, suggesting that the association between the sense of agency and 200ms delay is not trivial. Moreover, a closer look at the brain regions that proved to be significantly involved in the self-agency experience tells something about the nature of the sense of agency.

Firstly, the results highlighted the involvement of pre-SMA in agency-related intentional binding. There is independent evidence of a link between the pre-SMA and the sense of agency experience. For example, EEG evidence showed that voluntary movements following early readiness potentials - which has been related to the activity of the pre-SMA (Shibasaki and Hallett 2006) - result in a stronger binding effect compared to positive potentials (Jo et al. 2014). Non-invasive brain stimulation studies suggested that transcranial direct current stimulation over the pre-SMA reduces the intentional binding effect towards auditory outcomes (Cavazzana et al. 2015). In another study, continuous theta-burst stimulation over pre-SMA reduced the temporal linkage between a voluntary key-press action and a subsequent electrocutaneous stimulus (Moore et al. 2010a). Last, a study with patients with corticobasal syndrome underlined that the functional connectivity patterns between the pre-SMA and the prefrontal cortex change according to the intentional binding effect (Wolpe et al. 2014).

Crucially, although the spatial contiguity, recent data suggest essential distinctions between the SMA proper and the pre-SMA (Kim et al. 2010, Nachev et al. 2008, Picard and Strick 2001). SMA proper is a typical premotor area. It is somatotopically organized, it projects directly to

the spinal cord and the primary motor cortex (He et al. 1995), and it is functionally connected with regions related to simple motor control (Kim et al. 2010). Therefore, activations of the SMA proper when making voluntary movements of the hand are largely expected (please, see the effect of the comparison "Active condition > Passive conditions"). Conversely, pre-SMA is connected with the prefrontal cortices and high-level motor areas. It has a specific role in the execution of complex tasks, such as the alternation of motor plans, task switching, acquisition of new motor skills, and motor selection (Nachev et al. 2007, Nachev et al. 2008). Crucially, pre-SMA is also a key structure for preparing and initiating voluntary actions, showing greater activity for self-initiated movements compared with externally triggered actions (Cunnington et al. 2003, Zapparoli et al. 2018). Its electrical stimulation also causes a feeling of "urge" to move a specific body part in the absence of any detectable physical movement (Fried et al. 1991). All these considerations then suggest that pre-SMA is associated with higher-level motor functions than the mere movement execution (Nachev et al. 2007, Nachev et al. 2008). Among these, the generation of the sense of agency for the produced consequences of the movement. The specific role of the pre-SMA activity in the creation of the sense of agency is still unclear. One possibility is that the pre-SMA contributes to the self-agency experience using motor information (the so-called "efference copy") to generate *predictions* of the sensory consequences of the action (Frith et al. 2000, Wolpert, Ghahramani and Jordan 1995, Wolpert and Ghahramani 2000, Adams, Shipp and Friston 2013, Friston et al. 2013). According to the well-known Comparator model, predictions would then be compared with the real outcomes of the actions, which would be perceived as self-caused when there was a match between the predicted and experienced sensory effects (Blakemore et al. 2002, Frith et al. 2000).

Remarkably, the pre-SMA pattern of activation related to the intentional binding in this task was lateralized. This might not be surprising since activations were found in the left hemisphere, in a task where participants responded with their right hand. Therefore, one possibility is that pre-SMA uses lateralized motor information to generate predictions of the sensory consequences of the action. However, this hypothesis remains speculative and further studies are needed to rule out the possibility that these results could be somehow dependent on the specific features of analyses (e.g., the cluster-wise threshold applied to the statistical maps was $p<0.05$ FWER-corrected level).

Activations in the parietal lobules are not surprising. Neuroimaging studies have consistently highlighted the role of the parietal cortex in attributing agency. Most of these studies used explicit agency-attribution judgments in action recognition tasks, in which spatial or temporal distortion was added between participants' movement and the provided visual feedback. They consistently showed the activation of the inferior parietal cortex and the angular gyrus in conditions in which visual feedback was judged as no-self-generated, unrelated to participants' intention ("External-agency" condition, see for example Farrer and Frith 2002, Farrer et al. 2003, Farrer et al. 2008b). For example, in an early study, attributing action feedback to an external agent was associated with activation in the inferior parietal cortex (Farrer and Frith 2002). Likewise, right angular gyrus activity correlated with the magnitude of the discrepancy between the intended and the actual outcome of the action (Farrer et al. 2003). The link between the parietal lobules and the external agency attribution has been extensively demonstrated also by non-invasive brain stimulation studies. For example, Preston et al. (2008) showed that participants were more likely to erroneously misattribute agency to the computer compared to the self when transcranial magnetic stimulation (TMS) was applied over the inferior parietal cortex (Preston and Newport 2008). Similarly, Ritterband-Rosenbaum et al. (2014) showed that - following inferior parietal cortex rTMS stimulation - subjects showed the tendency to experience self-controlled movements as being externally perturbed (Ritterband-Rosenbaum et al. 2014). In another study, Chambon et al. (2015) demonstrated that TMS over the inferior parietal cortex at the time of action selection disrupts perceived control over subsequent effects of the action (Chambon et al. 2015). Importantly, in contrast to those previous studies showing a significant association between parietal activations and the external agency experience, in the present study, I found parietal activations for the self-agency experience, i.e., when participants perceived a stronger intentional binding effect. It follows that the activity in the parietal cortex could represent a general mechanism underlying the agency generation, including both self- and external agency attribution, rather than a specific neural substrate for the external agency as previously suggested. The proposal of the parietal cortex as a mismatch detector for visuomotor discrepancies (Sperduti et al. 2011) does not seem justified here. Instead, considering its notorious role in the high-order processing of sensory and multisensory inputs (Berlucchi and Vallar 2018), one may speculate that the parietal cortex may be responsible for the comparison between internal predictions and the external events to attribute a sense of agency for the action - a hypothesis that is inscribed within the concepts of the Comparator

model (Blakemore et al. 2002, Frith et al. 2000). This hypothesis would explain why a parietal activation can be observed in both self- and external agency attributions. It follows that while the pre-SMA may contribute to the generation of predictions before the action execution in a pre-motoric phase, the parietal lobule may play a role in a later phase when the consequences of the action are available to be compared with the predictions for the attribution of the sense of agency.

It is possible to hypothesize a role for other sensorimotor regions involved in the sense of agency with respect to the Comparator model (Blakemore et al. 2002, Frith et al. 2000). For example, the cerebellum might be involved in signaling the sensory discrepancy between the predicted and actual sensory consequences of movements. In an early study, Blakemore et al. (2001) used Positron Emission Tomography to examine neural responses to parametrically varied degrees of the discrepancy between the intended and actual sensory consequences of movement. They showed that the activity in the cerebellum exhibited a positive correlation with delay. As a consequence, they suggested that the cerebellum might have a role in detecting discrepancies between predictions and outcomes (Blakemore, Frith and Wolpert 2001). The insular cortex has been typically associated with sensorimotor integration (Cauda et al. 2011, Kurth et al. 2010b, Kurth et al. 2010a). Consequently, the insular cortex might contribute to the generation of a sense of agency, mainly by integrating different sources of information useful for comparison with predictions. However, fMRI does not have the temporal resolution needed for inferring the functional role of different brain regions within the broader agency system. It follows that all these interpretations remain speculative, and further studies taking advantage of different neuroscientific techniques are needed to support these claims.

Limitations

It is worth noting that the present study suffers from some limitations. For example, in the passive condition, participants' finger was pushed down by the experimenter. As a consequence, active and passive conditions are not completely comparable as there is additional tactile input in the passive condition. Other studies (see for example, van Kemenade et al. 2016) have overcome this limit by introducing alternative experimental manipulations in which the

button mechanically went down. However, these considerations were not such to prevent the observation of a meaningful relationship between fMRI brain activity and the sense of agency.

Conclusions

In conclusion, in this study, I characterized the subjective experience of agency using a distortion in time perception following voluntary action (i.e., the intentional binding effect), which is taken as a putative implicit marker of the sense of agency. I showed that the sense of agency strongly depends on the coupling between voluntary actions and effects, with a prominent role of the time delay between them. I also showed that a wide brain network correlated with the strength of the effect. This brain network includes both premotor areas that control intentional action (pre-SMA) and the sensorimotor areas (parietal lobule, insular cortex, and cerebellum) that integrate different sensory information to monitor the external consequences of the action.

Appendix

Table A1 | Results of the comparison Active > Passive conditions (independently from the different action-outcome delay). *p<0.05 FWER corrected (voxel level), ° p<0.05 FWER corrected (cluster level).

	MNI coordinates											
Brain regions (BA)	**Left hemisphere**						**Brain regions (BA)**					
	x	**y**	**x**	**Z-score**	**x**	**Cluster size**	**x**	**y**	**x**	**Z-score**	**x**	**Cluster size**
Inf Front Gyrus pars opercularis (44)	--	--	--	--	--	--	38	6	34	4.30°	p<0.0001	800
	--	--	--	--	--	--	48	10	30	3.74°	p<0.0001	
	--	--	--	--	--	--	50	10	24	3.69°	0.0001	
	--	--	--	--	--	--	44	12	28	3.39°	0.0003	
	--	--	--	--	--	--	44	12	36	3.17°	0.0008	
Mid Front Gyrus (46)	--	--	--	--	--	--	40	30	42	4.36°	p<0.0001	800
	--	--	--	--	--	--	38	44	24	4.37°	p<0.0001	
	--	--	--	--	--	--	38	38	28	3.90°	p<0.0001	
Mid Front Gyrus (9)	--	--	--	--	--	--	48	16	42	3.26°	0.0006	502
Mid Front Gyrus (8)	--	--	--	--	--	--	32	8	60	3.28°	0.0005	502
Mid Front Gyrus (6)	--	--	--	--	--	--	38	2	60	3.49°	0.0002	502
Sup Front Gyrus (6)	--	--	--	--	--	--	30	4	64	3.27°	0.0005	502
Sup Med Front Gyrus	--	--	--	--	--	--	2	32	44	3.56°	0.0002	2015
	--	--	--	--	--	--	0	36	40	3.40°	0.0003	
Ant cingulum (32)	--	--	--	--	--	--	0	36	28	3.43°	0.0003	2015
Middle cingulum (32)	--	--	--	--	--	--	10	12	38	5.07°*	p<0.0001	2015
	--	--	--	--	--	--	8	16	40	5.06°*	p<0.0001	
	--	--	--	--	--	--	2	34	32	3.28°	0.0005	
Middle Cingulum	-2	-10	48	5.09°*	p<0.0001	2015	10	4	46	4.21°	p<0.0001	2015
	-4	-6	48	4.88°*	p<0.0001		--	--	--	--	--	--
Pre-SMA	-2	2	50	3.94°	p<0.0001	2015	0	12	46	5.09°*	p<0.0001	2015
	--	--	--	--	--	--	0	16	44	5.03°*	p<0.0001	
Pre-SMA (6)	--	--	--	--	--	--	12	0	48	4.23°	p<0.0001	2015
	--	--	--	--	--	--	6	0	62	3.58°	0.0002	
SMA	--	--	--	--	--	--	0	-12	52	5.04°*	p<0.0001	2015
SMA (6)	--	--	--	--	--	--	6	-6	68	3.38°	0.0004	2015

Precentral Gyrus	--	--	--	--	--	--	52	10	38	3.94°	p<0.0001	800
	--	--	--	--	--	--	50	6	28	3.77°	p<0.0001	
Precentral Gyrus (6)	--	--	--	--	--	--	36	-12	42	4.36°	p<0.0001	502
	--	--	--	--	--	--	44	-6	56	3.95°	p<0.0001	
	--	--	--	--	--	--	44	-12	56	3.75°	p<0.0001	
	--	--	--	--	--	--	44	-14	48	3.71°	0.0001	
	--	--	--	--	--	--	48	-10	48	3.47°	0.0003	
	--	--	--	--	--	--	40	-14	62	3.30°	0.0005	
Precentral Gyrus (4)	-34	-24	60	6.94°*	p<0.0001	1056	32	-20	48	3.69°	0.0001	502
	--	--	--	--	--	--	42	-18	48	3.48°	0.0003	
Postcentral Gyrus	-50	-12	46	3.25°	0.0006	1056	44	-22	44	3.35°	0.0004	502
Mid Occ Gyrus (19)	-36	-82	-2	4.05°	p<0.0001	516	--	--	--	--	--	--
Inf Occ Gyrus (19)	-40	-80	-4	4.61°	p<0.0001	516	--	--	--	--	--	--
Fusiform gyrus (37)	-40	-68	-14	4.17°	p<0.0001	516	--	--	--	--	--	--
	-46	-54	-16	3.93°	p<0.0001		--	--	--	--	--	--
Cerebellum crus_1	-46	-54	-26	3.47°	0.0003	516	36	-66	-26	3.87°	p<0.0001	2781
	--	--	--	--	--	--	44	-66	-26	3.67°	p<0.0001	
	--	--	--	--	--	--	40	-66	-28	3.64°	p<0.0001	
	--	--	--	--	--	--	38	-46	-32	3.57°	0.0002	
Cerebellum vermis_6	--	--	--	--	--	--	2	-62	-12	4.62°	p<0.0001	2781
	--	--	--	--	--	--	2	-62	4	3.78°	p<0.0001	
Cerebellum vermis_4_5	--	--	--	--	--	--	0	-48	-20	3.59°	0.0002	2781
Cerebellum_4_5	-10	-58	-16	4.84°*	p<0.0001	2781	14	-46	-24	5.13°*	p<0.0001	2781
Cerebellum_6	-24	-58	-16	3.84°	p<0.0001	2781	28	-52	-20	4.56°	p<0.0001	2781
	-28	-60	-18	3.82°	p<0.0001		10	-64	-24	4.11°	p<0.0001	
	-26	-54	-20	3.76°	0.00008		10	-58	-18	4.09°	0.00002	
Cerebellum_8	--	--	--	--	--	--	12	-64	-32	4.27	0.00001	2781

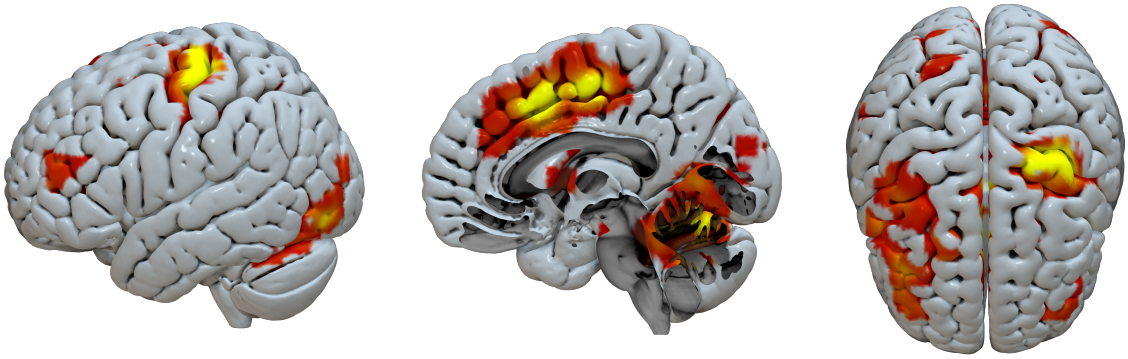


Figure A1 | fMRI Results: brain activation for the comparison Active > Passive conditions (independently from the different action-outcome delays).

Chapter 3

Study two: Modulating the sense of agency brain network with non-invasive brain stimulation[1]

Introduction

In the previous chapter, I explored the neural correlates of a distortion in time perception following intentional actions, which is taken as a putative marker of the self-agency experience. This effect is called "intentional binding" and consists of a perceived compression between the time of voluntary action and its subsequent sensory effect. I focused on those changes in time perception between a condition of intentional action and a control condition of passive movement. I showed that a significant difference between conditions is evident only at stringent action-outcome delays, precisely, when the voluntary action followed the outcome by 200ms. In this condition, a sizeable intentional binding effect also correlates with the activity of a wide

[1] This chapter contains experiments already published in:
Zapparoli, L*., S. Seghezzi*, E. Zirone, G. Guidali, M. Tettamanti, G. Banfi, N. Bolognini & E. Paulesu (2020) How the effects of actions become our own. Sci Adv, 6.

* shared first authorship

brain network, including both premotor areas that control intentional action (pre-SMA) and the sensorimotor areas (parietal lobule, insular cortex, and cerebellum) that integrate different sensory information to monitor the external consequences of the action.

However, fMRI does not permit me to make causal inferences on the relationship between local brain activity and behavioral effects. Neither does it have the temporal resolution needed for inferring the functional role of different brain regions within the broader agency system. Conversely, transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation technique that permits the study of causal relationships between the brain and the behavior by inducing a temporary and local modulation of the normal brain activity. The magnetic pulses produced by TMS determine a transient "virtual" lesion over a specific target area of the cortex, which can alter the participant's performance at a behavioral task of interest (Pascual-Leone et al. 1995). TMS has already been applied to the study of the brain correlates of the sense of agency. For example, Preston et al. (2008) showed that participants were more likely to misattribute agency to the computer compared to the self when TMS was applied over the inferior parietal cortex (Preston and Newport 2008). Ritterband-Rosenbaum et al. (2014) showed that - following inferior parietal cortex TMS stimulation - subjects showed the tendency to experience self-controlled movements as being externally controlled (Ritterband-Rosenbaum et al. 2014). Similarly, Chambon et al. (2015) demonstrated that TMS over the inferior parietal cortex at the time of action selection disrupts perceived control over subsequent effects of the action (Chambon et al. 2015). In another study, continuous theta-burst stimulation (cTBS) over pre-SMA was shown to reduce the temporal linkage between a voluntary key-press action and a subsequent electrocutaneous stimulus (Moore et al. 2010a). However, one crucial limit in these previous TMS studies is that the TMS target area was often identified from existing literature. For this reason, the authors could not ensure that the stimulated area was the same area responsible for the cognitive function being tested. Furthermore, some studies applied the stimulation before the task execution (MacDonald and Paus 2003, Moore et al. 2010a). For example, in Moore et al. (Moore et al. 2010a), the behavioral testing occurred after the cTBS, raising the problem of the specificity of the mechanism being modulated by offline TMS. Other studies chose online TMS protocol and applied the stimulation immediately before the movement execution (Ritterband-Rosenbaum et al. 2014), during the motor performance (Preston and Newport 2008), at the end of the executed movement (Weiss et al. 2014), or the appearance of the action consequences (Chambon et al. 2015). This heterogeneity, however,

makes previous results difficult to compare. Moreover, none of the aforementioned studies assessed the specific contribution of different brain areas at different time-windows of the agency generation process. The temporal resolution of the TMS is such that it is possible to explore discrete contributes of different brain areas in time, simply stimulating the cortex at different time points of the trial. However, to date, no study has taken advantage of this powerful method to explore the neurobiological correlates of the sense of agency, leaving the functional characterization of the sense of agency brain network incomplete.

In this study, I investigated the neural correlates of the sense of agency by measuring the effects of locally interfering with the brain activity of the identified agency network on the self-agency experience. To this aim, I used a non-invasive repetitive transcranial magnetic stimulation (rTMS), a protocol that has consistently been shown to modulate the neural activity in the target brain regions (Tremblay and Gracco 2009, Mahayana et al. 2014, Ritterband-Rosenbaum et al. 2014). Two brain regions were selected: the left pre-supplementary motor area (pre-SMA) and the right inferior parietal lobule, using the local maxima of the previous fMRI results. The pre-SMA is primarily concerned with voluntary movement generation (Zapparoli et al. 2018, Lau et al. 2004). The parietal lobule is involved in the high-order processing of sensory and multisensory inputs and with the representation of the external space and the body (Berlucchi and Vallar 2018). It follows that both target regions can contribute to the sense of agency, but they can be distinguishable in terms of both their function and time of contribution. Precisely, while the pre-SMA can contribute to the sense of agency generation before the action execution in a pre-motoric phase, the parietal lobule may play a role in a later phase when the consequences of the action are available to be appreciated and integrated into a coherent representation of the self. I thus explored the effect of two different stimulation timing: before the action execution, time-locked to the trial instruction's presentation, and after the action execution, time-locked to the appreciation of the generated consequences.

I investigated the effect of modulating either the pre-SMA or the parietal site activity on the intentional binding effect (Haggard et al. 2002), adopting the same temporal judgment task used in the previous fMRI experiment. The task was administered to two independent samples of healthy participants (one for each timing of the stimulation).

Changes in the intentional binding effect resulting from the modulation of either of these areas were also compared with the effects of an occipital control site stimulation. The occipital cortex

is highly unlikely to be involved in the sense of agency. Hence, since the TMS stimulation induces a wide range of non-specific effects, such as auditory and cutaneous stimulation, the inclusion of a control stimulation ensured that any changes in intentional binding following the pre-SMA and/or parietal stimulations could reliably be interpreted as specific effects. It follows that if rTMS over either pre-SMA or the parietal lobule – but not over the occipital cortex - significantly affected the intentional binding, I will infer that such brain area has a causal role in the sense of agency generation. Moreover, if the modulative effect was specific for a precise time-window of stimulation, I will also infer the functional role of the relevant area in the sense of agency broad network.

Methods

Participants

Two samples of twenty healthy adult subjects (Experiment 1: mean age: 22.2 ± 2.6 years; mean education 14 ± 2.1 years; male: 5; Experiment 2: mean age: 24 ± 4.9 years; mean education 14.7 ± 2.3 years; male: 3) participated in this study. All participants were right-handed as assessed by the Edinburgh handedness inventory (Oldfield 1971). None of them had contraindications to TMS accordingly to TMS safety guidelines (Rossi et al. 2009, Rossi et al. 2011)

Before the experiment, each subject completed a brief neuropsychological screening. The neuropsychological battery included the Mini-Mental State Examination (MMSE, Folstein et al. 1975), the Raven's Colored Progressive Matrices (Raven's Matrices, Raven et al. 1998), and the Frontal Assessment Battery (FAB, Dubois et al. 2000). No subject reported pathological scores at any test.

Participants were selected from an initial larger sample of 60 participants. Subjects who did not show the intentional binding phenomenon at the baseline session were not recruited for the other experimental sessions. The logic behind this screening was as follows: an external intervention to modulate a behavioral effect can only be studied when the effect is present (Moore et al. 2010a).

The study protocol was approved by the local Ethics Committee (IRCCS *San Raffaele* of Milan; Prot. SOA, 149/INT/2016). Informed written consent was obtained from all subjects according

to the Helsinki Declaration (1964). All subjects participated in the study after the nature of the procedure had been fully explained.

Sample size calculation

I first performed a sample size calculation to estimate the sample size needed to reliably detect an effect. I took advantage of the data published by Moore and colleagues in 2010 (Moore et al. 2010a). Moore et al. (2010) investigated the TMS-induced modulations of the sense of agency using the intentional binding phenomenon as a dependent measure. Disruption of the pre-supplementary motor area was shown to reduce the binding effect between a voluntary action and a subsequent electrocutaneous stimulus. In contrast, TMS modulation of the sensorimotor leg area had no significant effect (mean post-TMS over pre-SMA: 118±22; mean post-TMS over the somatosensory leg area: 153±24ms). The effect size associated with this result was 1.07. Accordingly, a sample of 17 subjects is needed to reliably detect, with a power greater than 0.9, an effect size of $\delta \geq 1.07$, assuming a two-sided criterion for detection that allows for a maximum Type I error rate of $\alpha=0.01$. Based on this analysis, I then decided to include 20 participants for each experiment.

General procedure: Experiment 1 and Experiment 2

The experimental procedure was the same for both Experiments 1 and 2.

The experiment was performed in three sessions on three different days. At least 24 hours passed between one session and the other. Each session corresponded to a different stimulation site (for details, please see the section *Stimulation sites*). The stimulation order was counterbalanced between subjects.

In the first session, after given the informed consent, participants completed the Edinburgh Inventory (Oldfield 1971), the TMS safety checklist questionnaire (Rossi et al. 2011), the neuropsychological battery (MMSE, Folstein et al. 1975, Raven's Matrices, Raven et al. 1998, FAB, Dubois et al. 2000). In addition, they completed a training session composed of ten trials, during which they received feedback on their accuracy trial by trial.

Participants sat comfortably in a dark room, with the PC screen and the keyboard in front of them. An experimenter sat next to the participant for the entire duration of the experiment. This setting allowed the experimenter to press his/her right-hand index finger when the trial was

passive. At the beginning of each session, participants performed the task without TMS (please see the section *Experimental task*). At the end of this baseline session, the resting motor threshold was determined, and the target area(s) were found using the neuronavigation procedure described in detail below (please see the section *Coil placement procedure*). Then, participants performed the task a second time while TMS was applied (please see the section *TMS details*).

The timing of the TMS stimulations was digitally synchronized and triggered according to the experiment specifications (for details, please see the section *Stimulation timing*).

Experimental task

Participants performed the same temporal judgment task previously used in the fMRI experiment (chapter two).

In brief, the task consisted of active and passive trials. Each trial started with the presentation of the picture of a turned-off lightbulb on the screen. For the active trials, the base of the bulb was colored in green. For the passive trials, the base was colored in red. Participants were instructed to press a button with their right index finger every time they saw a green lightbulb (active trials). They were invited to make the press at their own time. This was done to elicit a well-prepared, self-initiated button press, rather than an automatic movement as a reflex to the instruction. They were instructed to refrain from acting when the base of the lamp was colored in red (passive trials). In this case, the experimenter present inside the MRI room pressed participants' right index finger to induce a passive movement. In both conditions, the button press caused the illumination of the lamp. This could happen after 200, 400, or 600 milliseconds (ms) of delay. The feedback lasted 500ms. After 2000ms, participants judged the perceived time interval between the button press and the illumination of the lamp. Judgments were reported by means of a visual analog scale at which they responded using a five-key response keypad placed under their left hand. They used their fingers to select one of five possible response options: 1ms, 200ms, 400ms, 600ms, and 800ms. The lowest and the highest response options were included to make it possible for the participants to underestimate and overestimate each presented time interval.

The task consisted of 60 trials, equally distributed between active and passive conditions, with ten trials for each delay. The inter-stimulus interval randomly varied between 1500ms and 2500ms.

The task lasted approximately twelve minutes, depending on the individual reaction times. The task structure was event-related and interleaved.

Repetitive Transcranial Magnetic Stimulation (rTMS)

TMS details

TMS pulses were delivered by means of an Eximia™ TMS stimulator (Nexstim™, Helsinki, Finland) using a biphasic figure-of-eight coil (diameter: 70 mm).

During the experimental task, a rapid train of 5 TMS pulses was delivered with a frequency of 10 Hz. This high-frequency rTMS protocol is widely used in literature to modulate the response of the stimulated cortical areas (Tremblay and Gracco 2009, Mahayana et al. 2014, Ritterband-Rosenbaum et al. 2014).

As a value for the rTMS intensity (corresponding to the percentage of the Maximum Stimulator Output), I used the one that induces an electric field of at least 85≃90 V/m in the cortical target area. Induced electric field intensity (V/m) was estimated using the NBS system. This system identifies the locally best-fitting spherical mode, which accounts for each participant's head and brain shape and considers the distance from scalp and coil position. For more details on the stimulation intensities, please see **Table 1**.

Table 1 | Mean rTMS intensities (expressed as percentage of the maximum intensity deliverable by the TMS machine) and respective induced electric field (Mean ± SD). Within a single experiment, these intensities were not statistically different (Experiment 1: $F(2,38)=0.433$; $p=0.652$; Experiment 2: $F(2,38)=0.005$; $p=0.995$).

	Stimulated site		
	Pre-SMA	**Parietal site**	**V1**
Experiment 1	46.2 ± 4.4% *90.6 ± 10.7 V/m*	47.6 ± 3.1% *87.8 ± 7.1 V/m*	44.5 ± 4.8% *91.9 ± 9.7 V/m*
Experiment 2	46.4 ± 3.6% *86.8 ± 7.3 V/m*	47.4 ± 3.3% *86.1 ± 8.7 V/m*	45.5 ± 4.2% *88.1 ± 7.9 V/m*

Stimulation timing

In the first experiment (Experiment 1), rTMS was delivered before the action execution, time-locked to the appearance of the green or red turned-off lamp.

In the second experiment (Experimenter 2), rTMS was applied after the movement execution, time-locked to the lightening of the lamp.

The stimulation was applied for both active and passive conditions. Please see **Figure 1** for an illustration of the experimental structure.

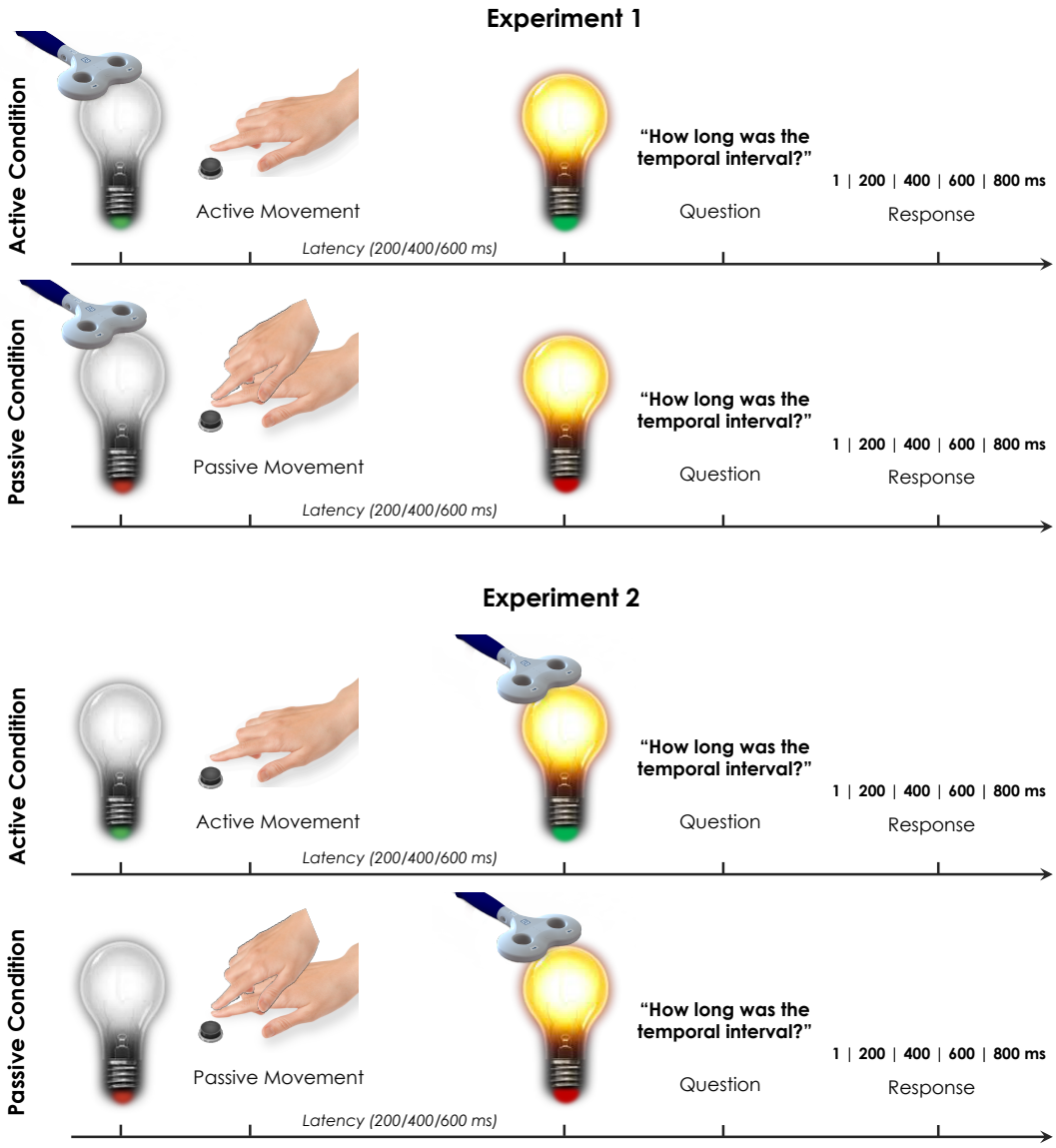


Figure 1 | Graphical illustration of the experimental structure. In Experiment 1, rTMS was applied before the action execution, time-locked to the appearance of the turned-off lamp. In Experimenter 2, rTMS was applied after the movement execution, time-locked to the lightening of the lamp. In the figure, the rTMS coils are placed according to the time points of rTMS delivery.

Stimulation sites

rTMS was delivered over the left pre-SMA and the right parietal cluster identified by the fMRI experiment and over an occipital control site. The coordinates of the stimulations for the pre-SMA and the parietal cluster were x=-16, y=12, z=64; and x=36, y=-40, z=66. These coordinates corresponded to the local maxima of the pre-SMA and parietal clusters, respectively.

To make sure that the pre-SMA stimulation does not interfere with the activity of the SMA proper, before the task execution, I checked for any visually detectable motor twitches in the contralateral right hand while pre-SMA was stimulated at the TMS intensity that induced an electric field of at least 85≃90 V/m in the cortical target area. No participant exhibited any twitches.

The coordinates of the occipital control site were x=-14, y=-100, z=7. These coordinates resulted from the previous fMRI literature (Plomp et al. 2015). For a graphical representation of the stimulation sites, please see **Figure 2**.

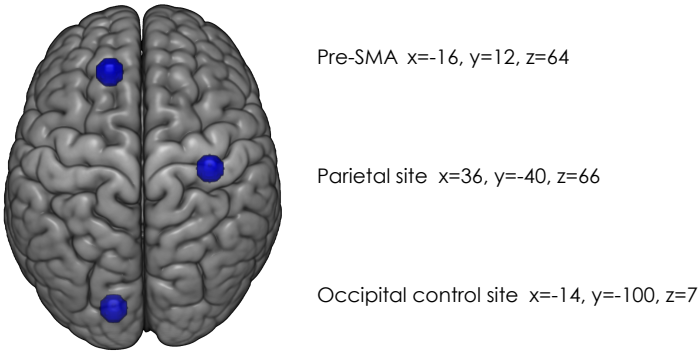


Figure 2 | Graphical illustration of the stimulation sites.

Coil placement procedure

MNI coordinates of the target areas were marked on the individual MRI using a stereotactic procedure.

In a preliminary session, I collected a standard volumetric T1 MRI (flip angle 35°, TE=5ms, TR=21ms, FOV=256 x 192 mm, matrix=256 × 256, TI= 768ms, for a total of 160 axial slices with 1 mm cubic voxels) for each subject. Then, the native (T1-weighted) image was normalized to the MNI space using SPM12 (SPM12, Wellcome Department of Imaging

Neuroscience, London, UK). After the normalization, the images underwent a signal subtraction process in the target loci using the aforementioned coordinates with a 2-mm radius sphere. The processed images were then transformed back to the native individual space using the backward deformation parameters estimated during the normalization procedure. For a graphical representation of the procedure, please see **Figure 3.**

The coordinates of interest were then localized on the individual MRI using the stimulator's integrated Navigated Brain Stimulation (NBS) system (Nexstim™, Helsinki, Finland), which employs infrared-based frameless stereotaxy in order to map the participant's head and the position of the coil, within the reference space of the individual MRI. Furthermore, I used this system to continuously monitor the position and orientation of the coil during the experiments, assuring precision and reproducibility of the stimulation within and across participants.

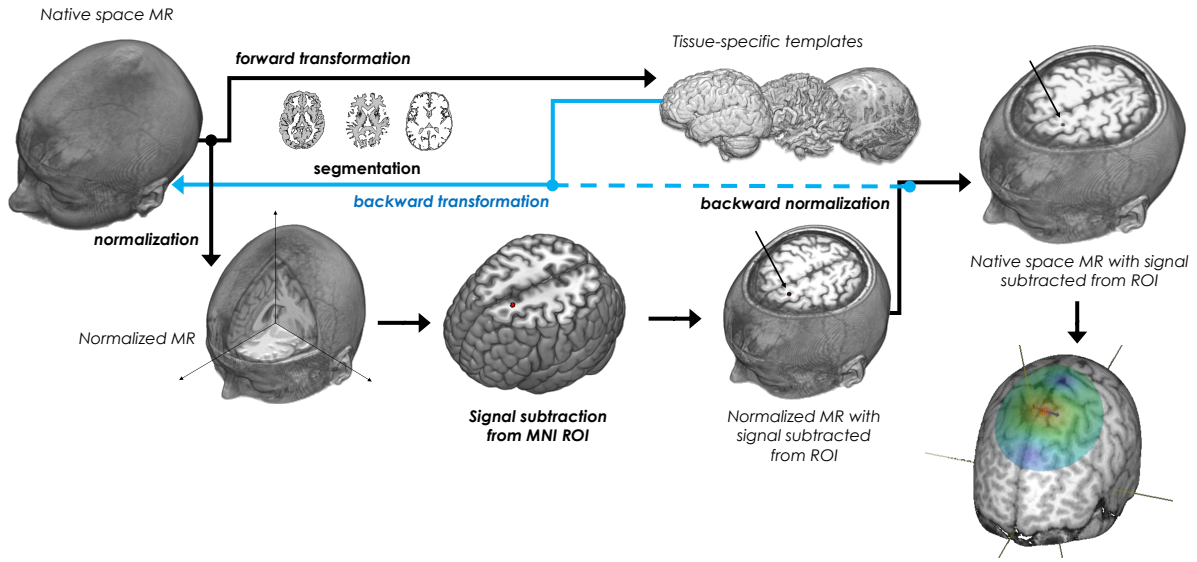


Figure 3 | Coil placement procedure. Adapted from "Stereotaxic coil placement made easy: a neuroimaging-based pipeline to determine coordinate-base stimulation sites for TMS". Bonandrini, R. and Seghezzi, S. Fourth NeuroMI-Milan Center for Neuroscience-International Meeting.

Statistical analyses of the behavioral data

Data were analyzed using the software SAS (Statistical Analysis System, version 9.4).
As in the fMRI experiment, in line with the description of the intentional binding phenomenon (Haggard et al. 2002), the "time compression" represented the indirect measure of the sense of agency, and it was entered into the model as the dependent variable. It refers to the difference between the estimated and the real duration of the action-outcome delay. Thus, more negative time compression values stood for stronger degrees of the perceived sense of agency.
The independent variables of the model were the factors "Session" (averaged baseline/rTMS over the pre-SMA/rTMS over the parietal site/rTMS over the occipital control site), "Condition" (active/passive), and "Delay" (200/400/600ms). The model was tested by using linear mixed models with random intercept. Significant interactions were further explored by means of planned Bonferroni corrected post-hoc comparisons.
Before applying linear mixed models, data distribution was inspected using the skewness-kurtosis graph of Cullen and Frey (Cullen and Frey 1999), which provides the best fit for an unknown distribution according to skewness level and kurtosis. The present data had a distribution similar to the normal distribution.

Results

Experiment 1

I found a significant "Condition*Delay" interaction ($F(2,4662)=39.02$; $p<0.0001$), a significant "Condition*Session" interaction ($F(3,4662)=2.91$; $p=0.03$), a significant "Session*Delay" interaction ($F(6,4662)=5.29$; $p<0.0001$) and a significant "Session*Condition*Delay" interaction ($F(6,4662)=2.18$; $p=0.04$). The main effects of the factors "Session", "Condition" and "Delay" were not significant (Session: $F(3,57)=0.24$; $p=0.87$. Condition: $F(1,4662)=0.01$; $p=0.91$. Delay: $F(2,38)=2.45$; $p=0.10$).
The significant "Session*Condition*Delay" interaction was further explored by means of planned Bonferroni corrected post-hoc comparisons. In brief, in all the experimental sessions at 200ms of delay, the perceived time compression was significantly stronger in the active trials compared with the passive ones. When the rTMS was applied over the pre-SMA, a significant

intentional binding effect was also observed at 400ms delay. For more details, please see **Table 2**. For a graphical representation of the results, see **Figure 4**.

Table 2 | Planned post-hoc comparisons between active and passive conditions at (a) 200, (b) 400, (c) 600ms delay. For each comparison, I reported the mean difference, the standard error (SE), the value of the statistic, the corresponding degrees of freedom (df), and the associated Bonferroni-corrected p-value. Asterisks indicate significant results at $p < 0.05$ Bonferroni corrected.

	Comparison											
	Session	**Condition**	**Delay**		**Session**	**Condition**	**Delay**	**Difference**	**SE**	**test**	**df**	**Bonferroni-corrected p**
a)	Baseline	Passive	200	-	Baseline	Active	200	48.18	15.26	3.16	4662	0.004*
	Pre-SMA	Passive	200	-	Pre-SMA	Active	200	50.87	15.26	3.33	4662	0.002*
	Parietal	Passive	200	-	Parietal	Active	200	36.88	15.26	2.42	4662	0.03*
	Occipital	Passive	200	-	Occipital	Active	200	41.9	15.26	2.74	4662	0.012*
b)	Baseline	Passive	400	-	Baseline	Active	400	-16.01	15.26	-1.05	4662	p>.99
	Pre-SMA	Passive	400	-	Pre-SMA	Active	400	34.97	15.26	2.29	4662	0.04*
	Parietal	Passive	400	-	Parietal	Active	400	9.02	15.26	0.59	4662	p>.99
	Occipital	Passive	400	-	Occipital	Active	400	-9.99	15.26	-0.65	4662	p>.99
c)	Baseline	Passive	600	-	Baseline	Active	600	-85.99	15.26	-5.63	4662	p>.99
	Pre-SMA	Passive	600	-	Pre-SMA	Active	600	-54.99	15.26	-3.60	4662	p>.99
	Parietal	Passive	600	-	Parietal	Active	600	-5.00	15.26	-0.33	4662	p>.99
	Occipital	Passive	600	-	Occipital	Active	600	-56.00	15.26	-3.67	4662	p>.99

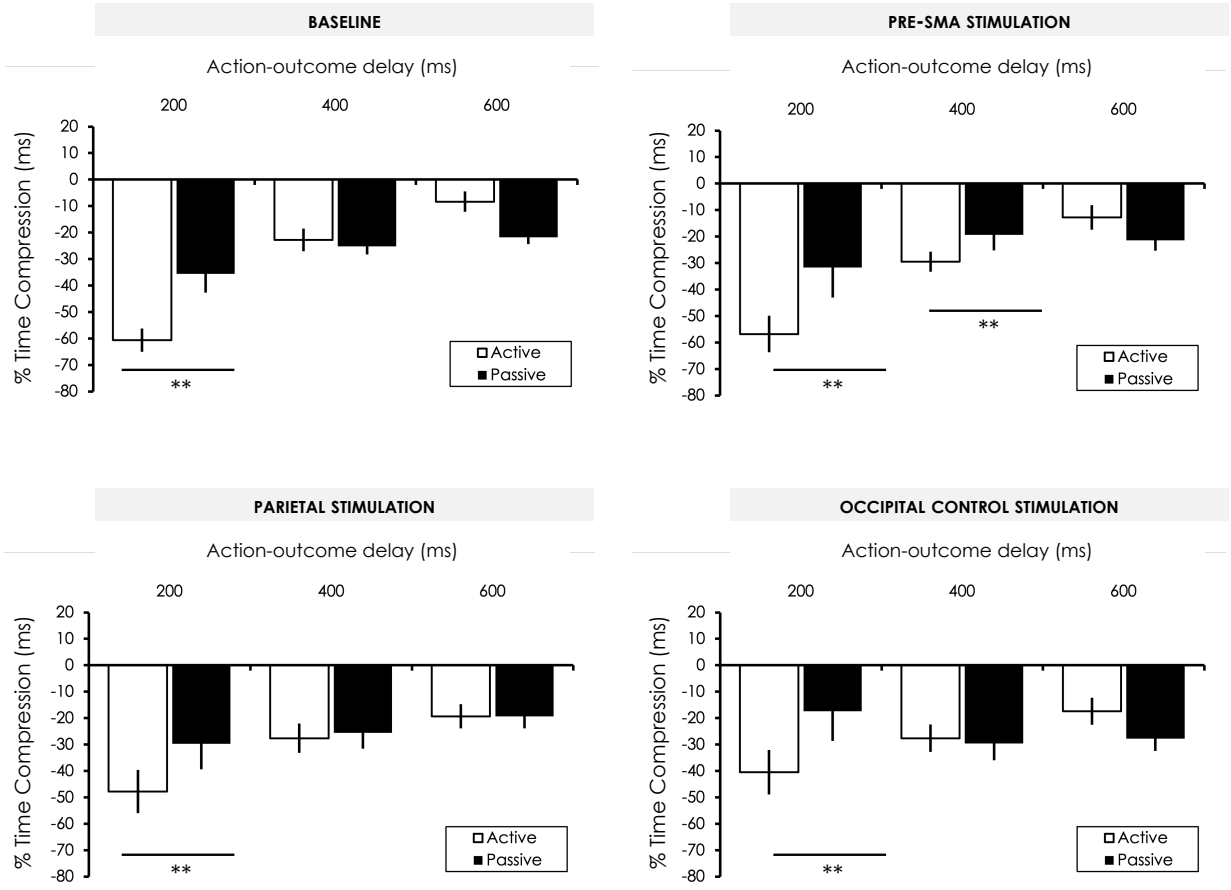


Figure 4 | Results of rTMS Experiment 1, i.e., when rTMS was applied before the action execution. (Error bars = standard errors; asterisks indicate significant effects; $p<0.05$ Bonferroni corrected). Time compression is visualized as the percentage of the time delay of the outcome (for visualization only).

Experiment 2

I found a significant effect of the factor Condition ($F(1,4662)=5.63$, $p=0.018$), a significant Condition*Delay interaction ($F(2,4662)=26.47$, $p< 0.0001$), a significant Condition*Session interaction ($F(3,4662)=2.66$, $p=0.046$), and a significant Session*Delay interaction ($F(6,4662)=6.57$, $p< 0.0001$). The main effects of the factors Session and Delay were not significant (Session: $F(3,57)=0.06$, $p=0.98$; Delay: $F(2,38)=1.04$, $p=0.36$); the triple interaction Session*Condition*Delay was not significant as well ($F(6,4662)=1.16$, $p=0.33$).

Planned post hoc comparisons showed that in all the experimental sessions, the perceived Time compression was stronger in the active than passive conditions at 200ms of delay. The same comparison was not significant at longer delays for any stimulation session. For more details, please see **Table 3**. For a graphical representation of the results, see **Figure 5**.

Table 3 | Planned post-hoc comparisons between active and passive conditions at (a) 200, (b) 400, (c) 600ms delay. For each comparison, I reported the mean difference, the standard error (SE), the value of the statistic, the corresponding degrees of freedom (df), and the associated Bonferroni-corrected p-value. Asterisks indicate significant results at $p < 0.05$ Bonferroni corrected.

	Comparison											
	Session	**Condition**	**Delay**		**Session**	**Condition**	**Delay**	**Difference**	**SE**	**test**	**df**	**Bonferroni-corrected p**
a)	Baseline	Passive	200	-	Baseline	Active	200	39.52	14.84	2.66	4662	0.016*
	Pre-SMA	Passive	200	-	Pre-SMA	Active	200	53.83	14.84	3.63	4662	0.0006*
	Parietal	Passive	200	-	Parietal	Active	200	48.89	14.84	3.29	4662	0.002*
	Occipital	Passive	200	-	Occipital	Active	200	48.85	14.84	3.29	4662	0.002*
b)	Baseline	Passive	400	-	Baseline	Active	400	-8.67	14.84	-0.58	4662	p>.99
	Pre-SMA	Passive	400	-	Pre-SMA	Active	400	17.99	14.84	1.21	4662	0.46
	Parietal	Passive	400	-	Parietal	Active	400	8.03	14.84	0.54	4662	p>.99
	Occipital	Passive	400	-	Occipital	Active	400	27.93	14.84	1.88	4662	0.12
c)	Baseline	Passive	600	-	Baseline	Active	600	-85.99	14.84	-5.63	4662	p>.99
	Pre-SMA	Passive	600	-	Pre-SMA	Active	600	-20.01	14.84	-1.35	4662	0.36
	Parietal	Passive	600	-	Parietal	Active	600	6.00	14.84	0.40	4662	p>.99
	Occipital	Passive	600	-	Occipital	Active	600	-38.98	14.84	-2.63	4662	p>.99

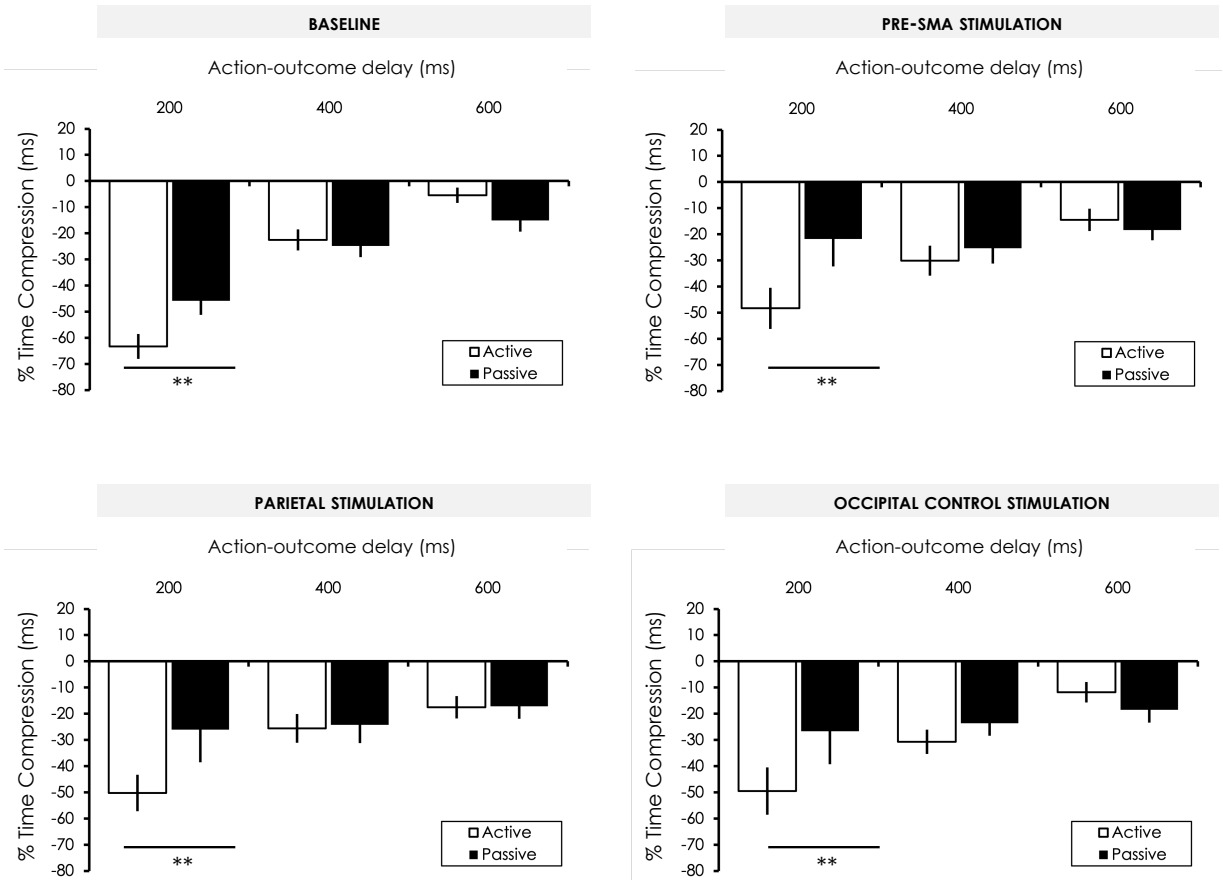


Figure 5 | Results of rTMS Experiment 2, i.e., when rTMS was applied after the action execution. (Error bars = standard errors; asterisks indicate significant effects; $p<0.05$ Bonferroni corrected). Time compression is visualized as the percentage of the time delay of the outcome (for visualization only).

Discussion

In this study, I used rTMS to explore the neural substrates of the sense of agency. To this aim, two target brain areas were stimulated: the left pre-supplementary motor area (pre-SMA) and the right inferior parietal lobule, identified using the local maxima of the previous fMRI findings (please, see chapter two). I explore the effect of two different timing of stimulation: before the action execution, time-locked to the trial instruction's presentation, and after the action execution, time-locked to the appreciation of the generated consequences. I investigated the effect of modulating either the pre-SMA or the parietal target area activity on the intentional binding effect, the perceived compression between the time of voluntary action and the time of the following sensory effect (Haggard et al. 2002). I adopted the same temporal judgment task used in the previous fMRI experiment (chapter two), administered to two independent samples of healthy participants (one sample for each stimulation time).

The pre-SMA modulation before the action execution determined a significant change in the intentional binding, particularly in the time-window of its usual manifestation. Instead, modulating the parietal site with rTMS did not significantly affect the binding effect relative to baseline or the occipital control area stimulation. These results are discussed in detail below.

In the previous fMRI study (chapter two), I showed that individuals tend to perceive their voluntary actions and the subsequent outcomes as closer in time than a control condition in which the outcome follows a passive movement. However, this intentional binding effect strongly varies based on the time delay between the action and its sensory effect. While I observed a significant intentional binding effect at 200ms of delay, the same effect was greatly reduced at 400ms and absent at 600ms. In the present study, I showed that when rTMS was applied over the pre-SMA, participants showed the temporal marker of agency even for longer delays, expanding the time-window for the intentional binding effect from 200ms of delay up to 400ms.

The effect was *specific for the target pre-SMA area*. The stimulation of the parietal site or the occipital control site did not produce any significant change with respect to the baseline. As mentioned in the previous chapter, pre-SMA is a key structure for preparing and initiating voluntary actions, showing greater activity for self-initiated movements than externally triggered actions (Cunnington et al. 2003, Zapparoli et al. 2018). Its electrical stimulation causes a feeling of "urge" to move a specific body part in the absence of detectable physical

movements (Fried et al. 1991). Moreover, attending to the intention to move activates this area (Lau et al. 2004). This evidence suggests that the pre-SMA plays a crucial role in the experience of volition by representing the conscious intention to move. The present results indicate that the pre-SMA also has a role in the sense of agency generation. Precisely, in the previous fMRI study, I already showed that the pre-SMA activity significantly correlates with the intentional binding effect, the putative marker of the sense of agency. Stronger intentional binding effects were associated with higher activity of the pre-SMA. The present findings expand those previous results by showing that the pre-SMA also has a *causal* role in the sense of agency generation: modulating the pre-SMA activity before the action execution significantly affects the perceived association between actions and effects.

The effect was also *specific for the timing of the stimulation*. The stimulation of the same area after the motor execution did not produce any significant change with respect to the baseline. The specificity of the effect in time allows drawing some conjectures about the functional role of the pre-SMA in the sense of agency broad network. For example, one possibility is that pre-SMA contributes to the self-agency experience using motor information to generate *predictions* of the sensory consequences of the action. The role of predictions in motor control is widely recognized (Frith et al. 2000, Wolpert et al. 1995, Wolpert and Ghahramani 2000, Adams et al. 2013, Friston et al. 2013). Predicting the sensory consequences of the incoming movement is essential to accomplish the current motor programs and efficiently process the incoming sensory stimuli (Wolpert et al. 1995, Wolpert and Ghahramani 2000). Moreover, its role in attributing the external effects of self-generated movements to oneself has also been proposed (Blakemore et al. 2002, Frith et al. 2000). For example, Engbert and Wohlschläger (2007) assessed the impact of different outcome predictions on the perceived time of action. They manipulated the probability of the outcome so that in one condition, the probability of the outcome was high (80%); in the other condition, the probability was low (20%). They found stronger intentional binding in the higher outcome probability condition. Interestingly, the time of the action was shifted in time also in the absence of the outcome. These findings emphasized the role of predictions in the sense of agency: predicting the outcome was sufficient to induce binding, and the effect varied based on the generated predictions (Engbert and Wohlschläger 2007).

The hypothetical association between predictions and the pre-SMA is not new (see, for example Moore et al. 2010a). A predictive role is consistent, for example, with subdural recordings from

the pre-SMA. Ikeda et al. (1999) have demonstrated the pre-SMA function in anticipating forthcoming stimuli, aside from motor preparation (Ikeda et al. 1999). Moreover, a predictive function for the pre-SMA is also coherent with other evidence suggesting the pre-SMA role in action preparation (Cunnington et al. 2003, Zapparoli et al. 2018).

In the present study, interfering with the activity of pre-SMA before the action execution may lead to less precise predictions about the outcome of the movement. Precisely, as I argued in the previous chapter (please, see the discussion of chapter two), a latency of about 200ms is the one that can be measured in real life between the time when the agent press an electricity light-switch and the time that a conventional light bulb takes to be fully on (Sivak et al. 1994). As a consequence, an intentional binding at 200ms was largely expected based on the hypothesis that the sense of agency is tuned to time intervals that mimic our previous experience for a given action and its usual effects. An intentional binding effect at 400ms could be explained as a less efficient predictive process that – when disrupted by the rTMS stimulation over the pre-SMA – does not provide precise predictions about the timing of the action-outcome[2]. This inefficient process may cause an extension of the temporal window of tolerance for the expected outcome of actions, leading participants to treat as self-generated delayed consequences that are normally rejected as non-self-induced. In this sense, the extension of the time window for the manifestation of the intentional binding should be considered a *disruption* of the effect, not an augmentation. However, this interpretation remains speculative, and further studies are needed to support this hypothesis.

The second important result of the present study is that modulating the parietal site with rTMS did not significantly affect the binding effect relative to baseline or the occipital control area stimulation. However, care is needed in interpreting this result. I hypothesized that both pre-SMA and the parietal target regions would contribute to the sense of agency, and they would be distinguishable in terms of both their function and time of contribution. Precisely, while I anticipated a pre-SMA contribution before the action execution, I expected the parietal lobule to play a role in a later phase when the consequences of the action are available to be appreciated and integrated into a coherent representation of the self. Indeed, the lack of evidence suggesting a role for parietal cortices in the putative comparative phase of the sense of agency generation is not sufficient to exclude the existence of a comparator in toto.

[2] Effects at 600ms are probably too remote to make the intentional binding effect expand in time that far.

On the one hand, the absence of any effect of the stimulation at the time of action consequences may be due to certain uncontrolled experiment features. For example, in principle, it would have been interesting to investigate the rTMS effect also on the cerebellar activation foci resulting from the fMRI experiment. However, these were too deep to realistically hope to achieve a selective modulation. The same considerations apply to other foci, as the hippocampus and the insulae. Finally, other explanations are still possible, as the choice of the stimulation parameters or the exact timing of the stimulation.

On the other hand, other interpretations might justify the lack of evidence of the parietal contribution to the comparative process of the sense of agency. One possibility is that the key neural correlate of the sense of agency lies in changes in the *connectivity patterns,* rather than the activity of discrete brain areas. Particularly, the sense of agency might arise in the exchange between the pre-SMA, which predicts the sensory consequences of the movement, and parietal areas, that underlie the monitoring of perceptual events (Haggard 2017). If this is the case, modulating one region at a time might not be enough to affect the process. This perspective offers a different research framework for the sense of agency investigation, focusing on testing parameters of brain connectivity between the pre-SMA and the parietal regions (for example, using Dynamic Causal Modelling analysis), rather than looking for discrete contributes of the different areas. Another possibility is that there might be several comparators for specific predictions and sensory evidence, while there is no need for a superordinate comparator. Instead, the comparison should be processed into the low-level (sensory) nodes in a distributed circuit underlying sensorimotor integration. If this is the case, future studies should focus on the activity of the primary sensory cortices rather than on multisensory areas. For a deeper discussion of the results, please see the general discussion (chapter six).

Conclusions

In conclusion, in the present study, I showed that the subjective experience of agency, as indexed by the temporal association between voluntary actions and effects, strongly depends on the activity of the pre-SMA. More specifically, I suggest that the pre-SMA contributes to the sense of agency housing the predictions about the consequences of the action. These results enhance our knowledge about the neural correlates of the sense of agency and tip in favor of a link between the self-agency experience, motor predictions, and the medial premotor cortex.

Chapter 4

Study three: The sense of agency and its neural correlates for different action-outcomes[1]

Introduction

In the previous chapter, I stressed the importance of the pre-motoric brain signals for the genesis of the sense of agency. I showed that the experience of being the agent of action puts down roots long before the appreciation of the results of the generated action, at the time when intentions arise in the agent. At this phase, the pre-SMA has a causal role in the sense of agency generation. Indeed, when stimulated with TMS, the individual sense of agency undergoes a significant change, becoming less precise in time. These results then suggest a strong link

[1] This chapter contains experiments already published in:
Seghezzi, S. & L. Zapparoli (2020) Predicting the Sensory Consequences of Self-Generated Actions: Pre-Supplementary Motor Area as Supra-Modal Hub in the Sense of Agency Experience. *Brain Sci,* 10.

between the sense of agency, the medial premotor cortex, and the role of the pre-motoric brain signals for the genesis of the sense of agency.

However, as mentioned in the introduction, the core of the sense of agency is the association between the intention and the outcome (Haggard 2017). To experience a sense of agency for an action, the content of the intention must produce a specific external event. In other words, the normal sense of agency must also involve the experience of an external sensory consequence, which has been achieved through one's own action.

The pivotal role of the outcome in developing a sense of agency is highlighted by the evidence that the subjective experience of voluntary action largely depends on the presence of an outcome. For example, Moore and Haggard (2008) showed that the action binding is increased when the action produces a specific external outcome vs. a condition in which the action does not produce any effect. This suggests that the action consequence retrospectively triggered a shift in the perceived time of action, affecting the perceived sense of agency (Moore and Haggard 2008). There is independent evidence of the critical role of the outcome in developing a sense of agency. For example, a plethora of studies showed that people tend to erroneously attribute their actions to another agent when the action-outcome is spatially or temporally distorted (see for example the seminal study of Farrer et al. 2008a). Other studies suggested that the distinctive features of the outcome also modulate the implicit markers of the sense of agency, like the sensory attenuation (Blakemore et al. 1998). For example, Reznik et al. (2015) showed that sensory attenuation only occurs when the intensity of sounds that resulted from the action was high. Conversely, when the intensity of self-generated sounds was low, perceived loudness was enhanced, and no sensory attenuation occurred (Reznik et al. 2015). To date, however, no study has investigated the effect of the outcome's distinctive features on the intentional binding measure of agency. More importantly, no study has explored whether the sense of agency brain network is modulated by specific features of the generated outcome. In a recent study, it has been suggested that the angular gyrus may be a supra-modal area in the *external-agency* experience. Van Kemenade et al. (2017) asked participants to perform button presses, which led to the presentation of either a visual stimulus, a tone, or both, with a variable delay after the button press. Participants then judged whether there was a delay between action and feedback. They showed that the activity in the angular gyrus positively correlated with the extent of the delay for both visual, auditory, and audio-visual action consequences, suggesting a supra-modal involvement of this area in the external agency experience (van Kemenade et al.

2017). However, to date, no study directly tested the *self-agency* experience for the same action with different action consequences.

The present study further explores the link between the brain and the sense of agency in a behavioral and fMRI experiment. In particular, I assessed the brain correlates of the sense of agency for different action consequences compared to those tested in the previous fMRI study. Specifically, while I used visual feedback before, the sensory effect produced by the voluntary action in this task was an auditory tone. I used an identical experimental paradigm based on a temporal judgment task administered to the same sample of participants.

I first looked for possible differences between the visual and auditory domains in the behavioral manifestation of the sense of agency experience, i.e., the intentional binding effect at different action-outcome delays. According to the previous literature on sensory attenuation (Reznik et al. 2015), I expected the intentional binding to be modulated by the specific features of the action outcome.

I then explore whether these possible differences could be mirrored by similar differences at the neural level. Precisely, in the first study of the present thesis (Chapter two), I showed that the sense of agency is associated with a specific brain network, including the left pre-supplementary motor area (pre-SMA) and the right parietal cortex, which activity was positively correlated with the magnitude of the intentional binding effect for visual outcomes. In the third chapter, I also showed that repetitive transcranial magnetic stimulation (rTMS) over the pre-SMA significantly affects the sense of agency, suggesting the crucial (and causal) role of this area in the genesis of the sense of agency. A similar causal relationship between local brain activity and sense of agency has not been demonstrated for the parietal site or any other cortical region. As a consequence, I restricted my investigation here to the SMA/pre-SMA cortex with specific predictions in mind. Precisely, one possibility is that the SMA/pre-SMA shows a supra-modal involvement in the self-agency attribution, regardless of the specific features of the outcome. Accordingly, as for the visual consequences of actions, I would expect a similar correlation between the pre-SMA activity and the magnitude of the perceived compression between the time of the voluntary action and the subsequent auditory event. This would generalize the relationship between pre-SMA and sense of agency by excluding the possibility that previous results could depend on the specific features of the used paradigm. Alternatively, the pre-SMA activity seen in the previous fMRI task may depend on the specific

features of the used paradigm. In this case, I would expect no correlation between the pre-SMA and the sense of agency measure in the auditory task. In this case, different areas could correlate with the temporal linkage between actions and auditory consequences.
This experiment represents an important study needed to understand the mutual relationship between the brain and the external environment for the genesis of a sense of agency.

Methods

Participants

Participants were the same who were included in the first fMRI study of this thesis (chapter two).
From the initial sample of twenty-five healthy adult subjects (mean age: 25.7 ± 3.8 years; mean education: 15.6 ± 2.5 years; male/female: 12/13), one participant was eliminated from the fMRI analysis due to strong movement artifacts. The resulting 24 participants (mean age: 25.4 ± 3.5 years; mean education: 15.5 ± 2.5 years; male/female: 11/13) were all right-handed as assessed by the Edinburgh handedness inventory (Oldfield 1971).
Before the experiment, each subject completed a brief neuropsychological screening. The neuropsychological battery included the Mini-Mental State Examination (MMSE, Folstein et al. 1975), the Raven's Colored Progressive Matrices (Raven's Matrices, Raven et al. 1998), and the Frontal Assessment Battery (FAB, Dubois et al. 2000). No subject reported pathological scores at any test.
The study protocol was approved by the local Ethics Committee (IRCCS *San Raffaele* of Milan; Prot. SOA, 149/INT/2016). Informed written consent was obtained from all subjects according to the Helsinki Declaration (1964). All subjects participated in the study after the nature of the procedure had been fully explained.

Procedure

fMRI scans were acquired during the execution of a temporal judgment task with auditory stimuli. The task was performed in the same experimental session of the visual task (chapter two), in separated blocks. Blocks were presented in a counterbalanced order across participants to exclude any possible effect of the task order.

As for the visual task, the auditory had an event-related interleaved structure. It lasted for approximately twelve minutes.

Stimuli presentation was controlled by Cogent 2000 MATLAB Toolbox (MathWorks). Auditory stimuli were delivered through MRI-compatible headphones. Visual stimuli were presented using VisuaStim fiber-optic goggles (600x800 pixel resolution). Responses were recorded through response boxes placed under the participant's hands (Resonance Technology Inc., Northridge, CA, USA).

Experimental task

Participants performed a temporal judgment task, which consisted of active and passive trials. Each trial started with an auditory cue indicating the nature (active or passive) of the trial. During the active trials, participants pressed a button with their right index finger at their own time after the instruction's presentation. This was done to elicit a well-prepared, self-initiated button press, rather than an automatic movement as a reflex to the instruction. During the passive trials, participants were asked to stay still while an experimenter pushed down their index finger to induce a passive movement. In both conditions, the button press caused an action-consequence: a pure tone (1,000 Hz). This could happen after 200, 400, or 600 milliseconds (ms) of delay. The feedback lasted 500ms. After 2000ms, participants then judged the perceived time interval between the button press and the tone. Judgments were reported by means of a visual scale at which they responded using a five-key response keypad placed under their left hand. They used their fingers to select one of five possible response options: 1ms, 200ms, 400ms, 600ms, and 800ms. The lowest and the highest response options were included to make it possible for the participants to underestimate and overestimate each presented time interval. For a graphical representation of the task, see **Figure 1**.

The task consisted of 60 trials, equally distributed between active and passive conditions, with ten trials for each delay. The inter-stimulus interval randomly varied between 1500ms and 2500ms.

Before the experiment, subjects performed a training session composed of ten trials for each task, when they received feedback on their accuracy.

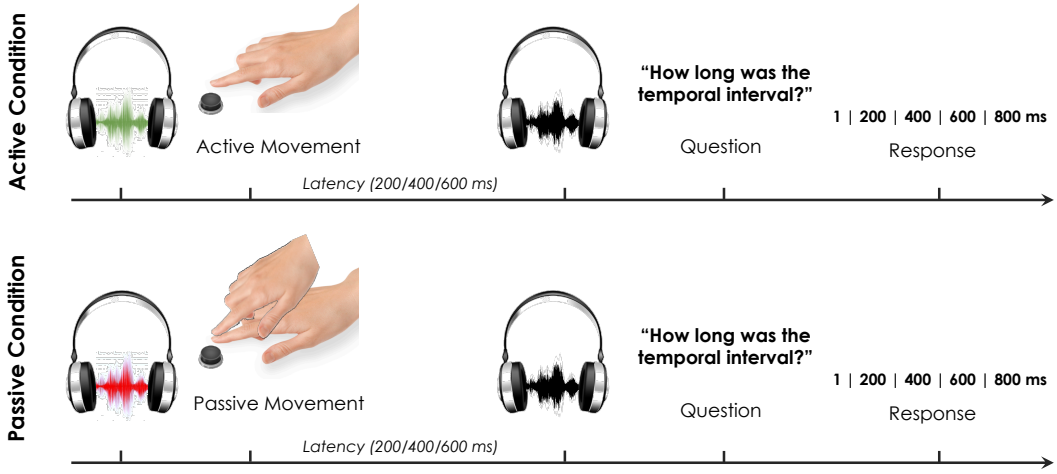


Figure 1 | Experimental task. Graphical illustration of an experimental trial for active and passive conditions. During the active trials, participants pressed a button with their right index finger at their own time after the presentation of the cue. In the passive trials, participants were asked to stay still while an experimenter pushed down their finger to produce a passive movement. In both conditions, the button press caused an action-consequence: a pure tone. The consequence was presented after a variable delay of 200, 400, or 600ms. Participants then judged the perceived time interval between their button press and the action-consequence.

Statistical analyses of the behavioral data.

Behavioral data collected during the fMRI experiment were analyzed using the software SAS (Statistical Analysis System, version 9.4).

In line with the description of the intentional binding phenomenon (Haggard et al. 2002), the time compression represented the indirect measure of the sense of agency and was entered into the model as the dependent variable. It refers to the difference between the estimated and the real duration of the action-outcome delay. Thus, more negative time compression values stood for stronger degrees of the perceived sense of agency. The independent variables of the model were the factors "Condition" (active/passive), "Delay" (200/400/600ms), and "Modality" (Visual/Auditory). The model was tested by using linear mixed models with random intercept. Significant interactions were further explored by means of planned Bonferroni corrected post-hoc comparisons.

Before applying linear mixed models, data distribution was inspected using the skewness-kurtosis graph of Cullen and Frey (Cullen and Frey 1999), which provides the best fit for an

unknown distribution according to skewness level and kurtosis. The present data had a distribution similar to the normal distribution.

fMRI data acquisition and analysis

MRI scans were acquired using a 1.5 T Siemens *Avanto* scanner, equipped with gradient-echo echo-planar imaging (flip angle 90°, TE=40ms, TR=2000ms, FOV=250 mm and matrix=64x64). The overall number of the collected fMRI volumes varied from 210 to 223 volumes depending on the individual reaction's times. The first 15 volumes of the block corresponded to the instructions' presentation and were discarded from the analyses.

Pre-processing

After the image reconstruction, raw data visualization, and conversion from DICOM to the NIFTI format were performed with MRIcron (www.mricro.com) software. All the subsequent data analyses were performed in MATLAB R2014a (Mathworks Natick MA USA) using the software Statistical Parametric Mapping (SPM12, Wellcome Department of Imaging Neuroscience, London, UK).

fMRI scans were realigned to the first image of the run to account for any head movement during the experiment. The structural T1 image was coregistered to the functional mean image to allow a more precise normalization. Then, the unified segmentation and nonlinear warping approach of SPM12 was applied to normalize structural and functional images to the MNI (Montreal Neurological Institute) template to permit group analyses of the data (Ashburner and Friston 1999, Friston et al. 1995). The data matrix was interpolated to produce 2 x 2 x 2 mm voxels. The stereotactically normalized scans were finally smoothed using a Gaussian filter of 10 x 10 x 10 mm to improve the signal-to-noise ratio and make the data suited for cluster-level correction for multiple comparisons (Flandin and Friston 2017).

The BOLD signal associated with each experimental condition was analyzed by a convolution with a canonical hemodynamic response function (HRF) (Worsley and Friston 1995). Global differences in the fMRI signal were removed from all voxels with proportional scaling. High-pass filtering (128s) was used to remove artefactual contributions to the fMRI signal.

First level fixed-effect analyses

A fixed-effect block-design analysis was performed for each subject to characterize the BOLD response associated with the task.

In particular, the brain activity between the appearance of the auditory instruction and the action-consequence (the tone) was separately specified for each condition (active and passive conditions) and each action-outcome delay (200/400/600ms), for a total of six regressors.

The brain activity occurring between the appearance of the evaluation scale and the response was similarly specified, separately for each condition and delay (for a total of six regressors) and added to the statistical model as non-interest regressors. In addition, the parameters obtained from the realignment procedure were added to the model to partial out the impact of motion artifacts on the estimates of the beta parameters.

For each subject for each action-outcome delay, I then generated a contrast image of the comparison Active condition > Passive condition, for a total of three contrast images per participant.

Second level linear regression analyses

The contrast images (Active condition > Passive condition) were entered in three separate second level linear regression analyses, conforming to a random-effect approach (Holmes and Friston 1998).

I performed three separate linear regression analyses, one for each action-outcome delay, to test the hypothesis that the activity of some brain regions covaried with the measured sense of agency (Time compression) in specific time-windows. It is important to note that, because the contrast images used in this analysis contained the differential effect between active and passive trials (Active condition > Passive conditions at the specific action-outcome delay), differential Time compression values between active and passive trials (mean time compression in the Active condition – mean time compression in the Passive conditions at the specific action-outcome delay) was used as a regressor here. I then compared the correlation coefficients obtained for each delay by using the Fisher r-to-z transformation.

Given the strong a-priori hypothesis, I focused the second-level analyses on SMA only. I used as an explicit mask a region of interest, created using bilateral anatomical masks based on the automated anatomical labeling (AAL) atlas (Tzourio-Mazoyer et al. 2002) of SMA.

All the reported results survive a correction for multiple comparisons: I used the nested-taxonomy strategy recommended by Friston et al. (Friston et al. 1996), including regional effects meeting either a cluster-wise or voxel-wise FWER correction. The voxel-wise threshold applied to the statistical maps before the cluster-wise correction was $p<0.001$ uncorrected, as recommended by Flandin and Friston (Flandin and Friston 2017). For clusters significant at the $p<0.05$ FWER-corrected level, I also report the other peaks at $p<0.001$.

Results

Behavioral Results

I found a significant effect of the factor "Condition" ($F(1,2614)=18.7$; $p<0.0001$), "Delay" ($F(2,2614)=28.23$; $p<0.0001$) and "Modality" ($F(1,2614)=10.53$; $p=0.003$) and a significant "Condition*Delay*Modality" interaction ($F(2,2614)=3.33$; $p=0.04$). The interactions "Condition*Delay" ($F(2,2614)=2.44$; $p=0.09$), "Condition*Modality" ($F(1,2614)=0.35$; $p=0.56$) and "Delay*Modality" ($F(2,2614)=0.04$; $p=0.96$) were not significant.

The Condition*Delay*Modality interaction was explored with planned post-hoc comparisons. Since the intentional binding effect is based upon specific differences in time compression between active and passive conditions (Haggard et al. 2002), whereby the passive condition represents the baseline, I explore differences in time compression values between active and passive conditions at different action-outcome delays, separately for each modality.

As seen in chapter two, in the visual task, the perceived time compression was significantly higher in the active trials compared with the passive ones when there was a temporal contingency of 200ms between the movement and the illumination of the lamp.

Conversely, in the auditory task, the perceived time compression was significantly stronger in the active trials compared with the passive ones at 400ms of delay between the movement and the tone. See **Table 1** and **Figure 2**.

Table 1 | Planned post-hoc comparisons between time compression values in the active and passive conditions at different action-outcome delays for each task. For each comparison, I reported the mean difference, the standard error (SE), the value of the statistic, the corresponding degrees of freedom (df), and the associated Bonferroni-corrected p-value. Asterisks indicate significant results at $p < 0.05$ Bonferroni corrected**.**

Comparison											
Condition	**Delay**	**Modality**		**Condition**	**Delay**	**Modality**	**Difference**	**SE**	**test**	**df**	**Bonferroni-corrected p**
Passive	200	Visual	-	Active	200	Visual	58.99	16.5	3.58	2614	0.002*
Passive	400	Visual	-	Active	400	Visual	32.37	16.4	1.98	2614	0.29
Passive	600	Visual	-	Active	600	Visual	-16.35	16.2	1.01	2614	p>0.99
Passive	200	Auditory	-	Active	200	Auditory	23.27	16.7	1.39	2614	p>0.99
Passive	400	Auditory	-	Active	400	Auditory	42.64	16.3	2.62	2614	0.048*
Passive	600	Auditory	-	Active	600	Auditory	32.67	16.4	2.00	2614	0.28

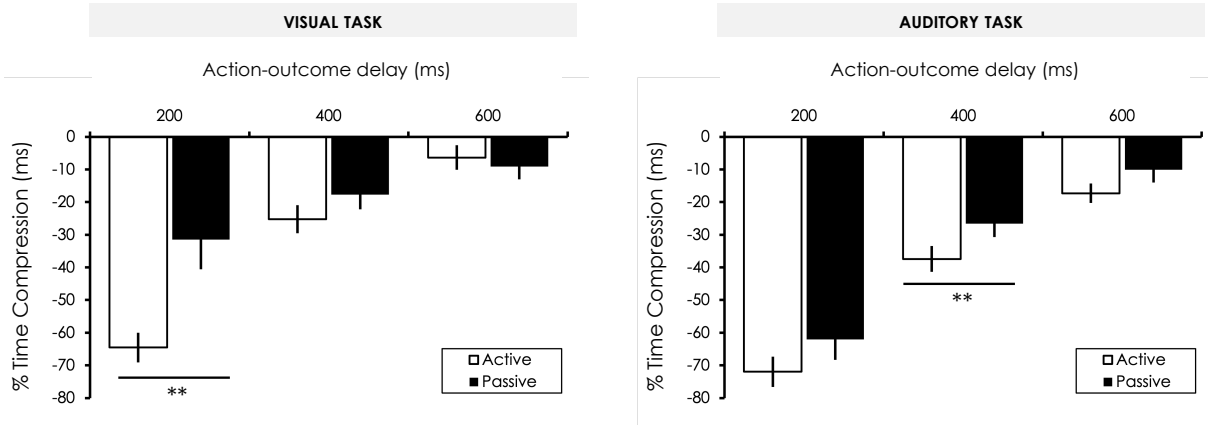


Figure 2 | Behavioral results showing the intentional binding effect at 200ms action-outcome delay for the visual task and the intentional binding effect at 400ms action-outcome delay for the auditory task. Error bars = standard error; asterisks indicate significant results at $p < 0.05$ Bonferroni corrected. Please note that the results are reported here as a percentage of the compression with respect to the action-outcome delay (for visualization only).

fMRI results

Linear regression analysis for the differential time compression values (active > passive trials) at 200ms action-outcome delay.

No cluster showed a significant relationship with the differential time compression values for 200ms of delays between action and the outcome. See **Figure 3a**.

Linear regression analysis for the differential time compression values (active > passive trials) at 400ms action-outcome delay.

I identified one cluster in the pre-SMA that showed a significant linear relationship between the differential time compression values of individual participants and the BOLD signal during the task (x=4, y=18, z=64, z score=3.75, FWE-corrected p=0.04, peak-level, FWE-corrected p=0.035, cluster-level). Specifically, more negative time compression values (estimated time interval shorter than the real interval, greater intentional binding) in the active than passive conditions were associated with higher BOLD response in this area. See **Figure 3b**.

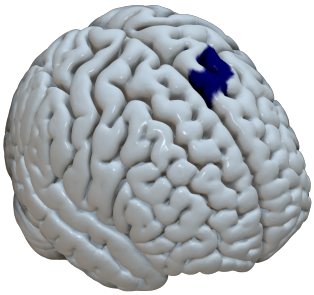
Linear regression analysis for the differential time compression values (active > passive trials) at 600ms action-outcome delay.

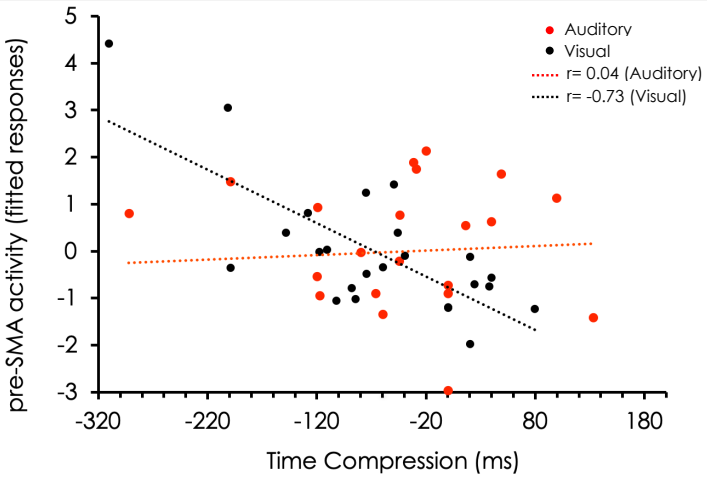
No cluster showed a significant relationship with the differential time compression values for 600ms of delays between action and the outcome. See **Figure 3c**.

The Fisher r-to-z transformation showed that the regression coefficient (r), indicating the strength of the association between the BOLD activity of the pre-SMA and the individually measured time compression values, was significantly higher for the 200ms of action-outcome delay than the same coefficients calculated for the 400 and 600ms of action-outcome delay (200ms r=-0.73, 400ms r=-0.0008, 600ms r=-0.004; 200ms r vs. 400ms r: z=-3.01, p-value=0.003; 200ms r vs. 600ms z=-3.00, p-value=0.003) in the visual task. Conversely, it was significantly higher for the 400ms of action-outcome delay than the same coefficients calculated for the 200 and 600ms of action-outcome delay (200ms r=0.04, 400ms r=-0.7, 600ms r=0.04; 200ms r vs. 400ms r: z=2.94, p-value=0.003; 400ms r vs. 600ms z=2.94, p-value=0.003) in the auditory task.

a. 200ms action-outcome delay

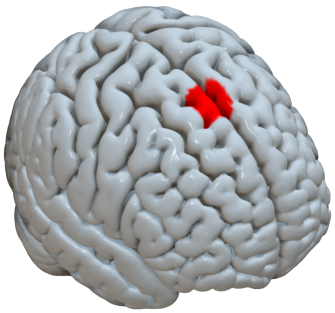
Voxels that show a significant correlation with the Time Compression in the **visual** condition at 200ms delay.

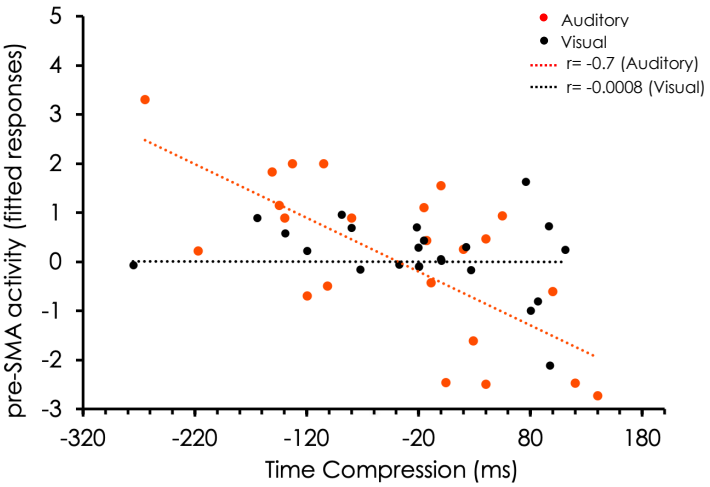




b. 400ms action-outcome delay

Voxels that show a significant correlation with the Time Compression in the **auditory** condition at 400ms delay.





c. 600ms action-outcome delay

No voxels show a significant correlation with the Time Compression at 600ms delay, in any sensory modality.

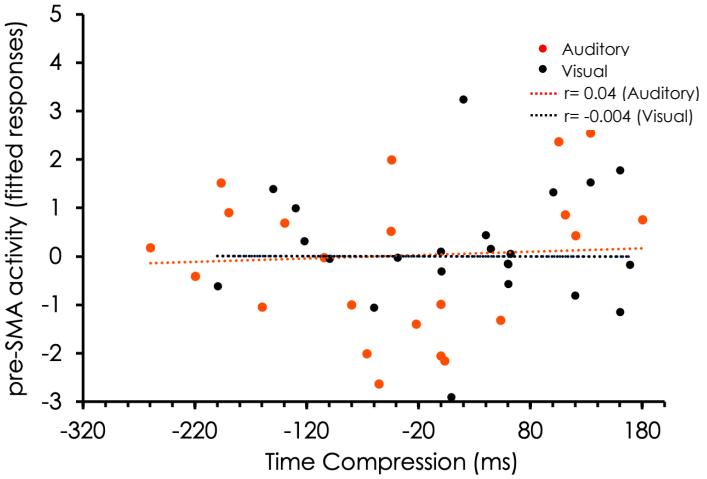


Figure 3 | Linear regression analysis between the pre-SMA activity during each task (fitted responses, active > passive conditions) and the differential time compression values (active trials - passive trials) when the action-outcome delay was 200ms (a), 400ms (b) and 600ms (c).

Discussion

The present study further explores the link between the brain and the sense of agency in a new behavioral and fMRI experiment. In particular, I assessed the brain correlates of the sense of agency for different action consequences compared to those used in the previous fMRI study. Specifically, while I used visual feedback before, the sensory effect produced by the voluntary action in this task was an auditory tone. I used an identical experimental paradigm based on a temporal judgment task administered to the same sample of participants.

I first looked for possible differences in the subjective experience of agency for different action outcomes. I showed diverse time-windows for the sense of agency manifestation depend on the action effect. While in the previous study, I reported an intentional binding effect in the condition of a stringent 200ms temporal contiguity between the action and the visual outcome, here I observed a sizeable time compression when the auditory outcome followed the action by 400ms.

I then explore whether these possible differences could be mirrored by similar differences at the neural level. The results showed that the intentional binding effect's magnitude was mirrored by meaningful brain activity in the anterior portion of SMA (pre-SMA) also when the outcome was an auditory tone. Importantly, the correlation between pre-SMA activity and intentional binding was significant only at the action-outcome time-window when there was a sizeable difference in the perceived time compression between the active and passive conditions for the specific action-outcome (400ms for the auditory modality; 200ms for the visual modality).

These results provide novel insights concerning the neural substrates of the sense of agency while supporting the previous conclusions. In particular, these findings shed light on the crucial role of the action-outcome in the arising of the sense of agency. At the same time, they confirm the sense of agency as a constructive phenomenon anchored to the motor system's functioning.

Behavioral results

As mentioned, the behavioral results showed different time-windows for the sense of agency depending on the generated outcome. In particular, the agency experience seems to be "faster" for visual than auditory action-consequences. While in the previous study, I reported an

intentional binding effect at 200ms of delay between the action and the visual outcome, I observed here a later binding effect at 400ms of delay between the action and the auditory outcome.

At first sight, this effect may be surprising since auditory processing is generally considered to be faster than visual processing (Vroomen and Keetels 2010). Thus, one might expect participants to show an earlier intentional binding effect for the auditory than the visual outcome. However, the intentional binding effect does not represent a pure perceptual phenomenon. Rather, several sources of information, such as high-level causal beliefs and expectations, all modulate this putative marker of the sense of agency (for a review see Moore and Obhi 2012).

While it looks implausible that there are precise time windows for the intentional binding in different sensory modalities, one possibility is that specific expectations about the outcome may determine the particular time window for the sense of agency to occur. These outcome expectations could derive from our prior experiences with specific action-outcome associations, and precisely from the repetition of the same association until a pattern of regularity is consolidated in the memory. This hypothesis is in line with previous studies showing that both agency's explicit and implicit measures are sensitive to the action-effect patterns to which people are exposed. For example, Hearing et al. (2015) showed that when participants were exposed to immediate action-effects, they felt less in control, the longer the delay between the action and the effect. In contrast, participants who were exposed to delayed effects showed the reversed result pattern and sensed less agency, the shorter the delay between action and effect (Haering and Kiesel 2015). Similarly, Kilteni et al. (2019) found that, after exposure to systematic delays, participants experienced less sensory attenuation for non-delayed self-generated touch. Conversely, they perceived as less intense - and thus attenuated - the delayed self-generated stimuli to which they were exposed (Kilteni, Houborg and Ehrsson 2019). It follows that the sense of agency seems to be tuned to time intervals that mimic the previous experience for a given action and its usual effects.

Crucially, one should consider that the visual stimuli used in the previous fMRI study had a clear link to real-life situations: indeed, a latency of about 200ms is the one that can be measured in real life between the time when we press an electricity light-switch and the time that a conventional light bulb takes to be fully on (Sivak et al. 1994). A binding effect at 200ms of action-outcome delay is thus in line with the suggestion that a sense of agency emerges for

action consequences that happen at action-outcome delays that are compatible with the expectations we made based upon our previous experiences (Frith et al. 2000, Wolpert et al. 1995, Wolpert and Ghahramani 2000). Instead, the auditory stimuli I adopted here (a pure tone) lacked any ecological meaning. As a consequence, participants could not rely on precise previous experiences with the stimulus, but only on a general expectation towards auditory outcomes. It follows that I cannot disentangle here whether the results are due to different previous expectations (in this case, general expectations about the association between a button press and any auditory stimulus) or a more general difference in the sensory modality. Importantly, while the same effect was described by Kuhn et al. (2013), who showed a significant auditory intentional biding effect at 400ms delay (Kühn et al. 2013), other intentional binding experiments described the effect also at 250ms action-tone delay (Jo et al. 2014), providing support to the hypothesis of different time windows for the intentional binding associated to specific action-outcome associations. However, future studies should orthogonalize these factors to explore the specific contribution (if any) of both the outcome sensory modality and the previous expectations towards it.

Neurofunctional results

At a neurofunctional level, the intentional binding effect's magnitude was mirrored by meaningful brain activity in the anterior portion of SMA (pre-SMA) also when the outcome was an auditory tone. However, while in the previous study this association was significant at 200ms of delay between the action and its visual effect, in this study, this association was significant at 400ms of delay, i.e., when there was a sizeable difference in the perceived time compression between the active and passive conditions at the behavior level. No significant effects have been found at 200 and 600ms.

This evidence provided validation of the experimental approach, suggesting that the link between the pre-SMA activity and the agency experience is not trivial. Indeed, it rules out the possibility that previous results were linked to the specific time course of the movement related pre-SMA activation, or they were somehow dependent on specific features of the stimuli used to describe it. Conversely, the pre-SMA activity seems to be specifically anchored to the subjective feeling of agency towards self-generated outcomes across modalities. This evidence provides support to the view that the brain mechanisms that give rise to our sense of agency are

strictly motoric (Frith et al. 2000, Wolpert et al. 1995, Wolpert and Ghahramani 2000), completing the circle of a conceptual validation of the sense of agency as a phenomenon anchored to the functioning of the motor system (Seghezzi et al. 2019). Furthermore, it allows generalizing the relationship between pre-SMA and the sense of agency as *supra-modal*. Previous studies have already suggested a general link between the pre-SMA and the sense of agency experience by using visual, auditory (Jo et al. 2014, Kühn et al. 2013), and tactile stimuli (Moore et al. 2010a), raising the possibility of a supra-modal nature of this relationship. However, this research has mainly focused on the agency experience in a single sensory modality. None of the aforementioned neuroimaging studies directly tested the role of the pre-SMA on the self-agency experience across different modalities through the same task and involving the same experimental participants. I showed here that the correlation between the pre-SMA activity and the magnitude of the intentional binding effect remains valid in spite of the sensory modality of the outcome. Even more importantly, it is tuned to the specific time-window in which the agency experience can be observed at a behavioral level for the specific task, suggesting a meaningful association between the pre-SMA activity and the experience of agency.

Limitations

It is worth noting that the present study suffers from some limitations. For example, it's worth noting that the pre-SMA activation is not exactly the same for the visual and auditory tasks. I observed a mesial to left hemispheric activation for the visual outcome and more mesial hemispheric activation for the auditory outcome. Therefore, I cannot describe the association pre-SMA-agency as anchored to a limited set of specific voxels. Rather, I can suggest that the pre-SMA might be seen as a supra-modal *hub* in the agency generation.

Furthermore, the pre-SMA does not represent the unique brain area responsible for the agency attribution. Other brain areas were shown to be involved in this process, like the right parietal lobule, the insula, the cerebellum (please, see chapter two). Here I concentrate the analysis specifically on pre-SMA/SMA since, in the previous studies, this area turned out to be causally involved in the sense of agency generation (please, see chapter three), while other brain regions did not show a similar causal relationship with the agency experience when TMS was applied during the task (see for example the parietal cortex). However, I cannot exclude that other brain

regions might provide a similar supra-modal contribution to the sense of agency generation. Further studies should expand this investigation to other brain regions.

Conclusions

In conclusion, these findings suggest that attributing consequences of self-generated movements to our actions is based on similar mechanisms across different sensory modalities and that these mechanisms are strongly related to the functioning of the pre-SMA. However, the subjective experience is modulated by the distinctive features of the outcome, showing different time windows for the intentional binding effect based on the sensory modality of the outcome.

Chapter 5

Study four: Altered sense of agency in Gilles de la Tourette Syndrome[1]

Introduction

Beyond the endeavor to explain the neural basis of the sense of agency, there is also considerable interest in describing its dysfunctions.

As anticipated in chapter one, most of the research carried out so far has focused on schizophrenia (Synofzik et al. 2010, Haggard et al. 2003). However, aberrant experiences of agency are not restricted to schizophrenic patients. An altered sense of agency has been described in several neurological and psychiatric conditions (Frith et al. 2000, Moore and Fletcher 2012, Sato and Yasuda 2005). For example, disturbances of the sense of agency have been described in obsessive-compulsive behavior (Gentsch et al. 2012), borderline personality disorder (Colle et al. 2020), anosognosia for hemiplegia (Berti et al. 2005), Parkinson's disease

[1] This chapter contains experiments already published in:
Zapparoli, L., S. Seghezzi, F. Devoto, M. Mariano, G. Banfi, M. Porta & E. Paulesu (2020a) Altered sense of agency in Gilles de la Tourette syndrome: behavioural, clinical and functional magnetic resonance imaging findings. *Brain Communications,* 2.

* shared first authorship

(Moore et al. 2010b, Saito et al. 2017) and movement disorders (Moore et al. 2010b, Saito et al. 2017).

Influent lines of research have firmly claimed the linkage between disruptions in awareness of action and selective impairments of the sensorimotor network that generates and controls the motor performance (Blakemore et al. 2002, Frith et al. 2000, Frith 2012). This makes any disorder of motor control particularly attractive in the context of agency research. In particular, of greater interest are the movement disorders that cause either an excess of involuntary movement or a paucity of voluntary movements, unrelated to the patient's intention. They include Parkinson's disease, Gilles de la Tourette Syndrome, Corticobasal syndrome, and other peculiar conditions, like Psychogenic movement disorders.

Disorders of the sense of agency in those syndromes are dramatically common. For example, Parkinson's disease patients report less sense of self-agency than healthy subjects in explicit tasks (Saito et al. 2017), and, when medicated, they show an abnormally strong action-effect binding relative to controls (Moore et al. 2010b). Similarly, Corticobasal syndrome patients exhibit an increased temporal attraction of the action toward the subsequent tone in the more-affected hand relative to control subjects (Wolpe et al. 2014). Also, patients suffering from psychogenic movement disorders show abnormal subjective reports of agency (Nahab et al. 2017), as well as altered patterns of intentional binding (Kranick et al. 2013) and sensory attenuation (Pareés et al. 2014).

Gilles de la Tourette syndrome (GTS) has become a matter of subject for the agency investigation only recently. GTS is a childhood-onset movement disorder characterized by hyperkinetic movements called tics and abnormal vocalizations (Leckman et al. 2010). The voluntary or involuntary nature of tics is unclear (Cavanna and Nani 2013). Of note, several environmental factors can modulate both the severity form and the occurrence of tics. Stress and anxiety are the most common factors that induce and exacerbate tics. In contrast, when patients are relaxed or engaged in certain activities requiring concentration or physical effort, tic severity and frequency are attenuated (Cohen, Leckman and Bloch 2013). Moreover, most GTS patients report that tics are often preceded by "premonitory urges", namely uncomfortable sensory phenomena characterized by restlessness, pain, pressure, mounting tension, or vague discomfort, that can only be relieved by the tic expression, similar to the relief following scratching or sneezing. Importantly, most GTS patients can also voluntarily suppress their tics for a short while. This peculiar feature of the syndrome is such that the imperative nature of the

premonitory urge imposes the expression of the tic against the individual's will; however, the decision to actuate the tic is usually perceived as a voluntary response to the unpleasant sensation (Cavanna and Nani 2013). Cavanna et al. (2013) thus suggested that tics might be considered as "unvoluntary," halfway between voluntary and involuntary actions (Cavanna and Nani 2013). Furthermore, while the mechanisms underlying tic expression are still poorly understood, Cavanna and Nani (2013) hypothesized that tics might have the same neural substrates as voluntary acts, even though they are perceived as involuntary (Cavanna and Nani 2013). This interpretation suggests the view of Gilles de la Tourette syndrome as a movement disorder affecting the conscious experience of action and then makes GTS extremely fascinating for the investigation of the sense of agency.

In line with this hypothesis, a recent study explored the sense of agency in GTS patients (Delorme et al. 2016b). Delorme et al. (2016) asked participants to make judgments of control and performance after completing a computerized game in which they moved a cursor on a screen to catch some targets. The control over the cursor could be normal, disrupted, or artificially enhanced. Delorme et al. (2016) showed that GTS patients reported an illusory sense of agency when their performance was artificially enhanced, suggesting that they did not realize that they were not fully responsible for the outcome, and they instead inflated their judgment of agency (Delorme et al. 2016b).

These findings were based on explicit agency judgments made by the participants on their performance. However, as mentioned before, explicit measures of agency are vulnerable to consistent cognitive biases typical of self-report measures (Wegner and Wheatley 1999). Moreover, explicit judgments of agency are rare in everyday life. Instead, it has been discussed that our everyday experience of agency mostly relies on implicit feelings of being in control that flows in the background of our mind (Kühn et al. 2013). Given these limits, it has been recommended that the sense of agency should rather be studied by implicit measures (Haggard 2017). However, to date, no study has investigated the sense of agency in patients with Gilles de la Tourette syndrome using implicit measures of agency. Moreover, no study has yet addressed possible brain alternations specifically associated with a disorder of the sense of agency in GTS patients.

The present study then aimed to explore the subjective experience of agency, and its neurobiological correlates in a population of Gilles de la Tourette syndrome patients' adopting

an implicit measure of agency that has proved to be a powerful proxy for both the behavioral and neural investigation of the sense of agency through this thesis: the intentional binding effect (Haggard et al. 2002).
I used the same experimental paradigm based on a temporal judgment task administered to the healthy sample of participants in the first study of this thesis (chapter two). Then, data of the GTS patients were compared with healthy participants' behavioral and fMRI data.

Exploring the sense of agency disturbances in Gilles de la Tourette syndrome offers the unique opportunity to study the cognitive and brain mechanisms behind the sense of agency starting from the observation of a dysfunction in the sensorimotor system and investigating its possible long-term effects on the sense of agency functioning. This investigation also may offer, in return, some hints about the nature of the Gilles de la Tourette syndrome and may pave the way for possible interventions aiming at improving patients' functioning in society.

Methods

Sample size calculation

I carried out an a-priori power analysis to determine the sample size of the study. There are no studies in the literature investigating the sense of agency in Gilles de la Tourette syndrome patients using the intentional binding phenomenon. I thus used as a reference a published study addressing a similar topic in patients affected by a different movement disorder, namely Parkinson's disease (Moore et al. 2010b). The effect size relative to the difference between the intentional binding phenomenon in Parkinson's disease patients and healthy controls was 1.14. Based on these data, a sample of 40 participants (20 for each group) would allow detecting a significant difference in the intentional binding effect between groups, with a power of 0.8 and an alpha of 0.01. I then recruited 25 Gilles de la Tourette syndrome patients to take into account possible dropouts.

Participants

Twenty-five patients Gilles de la Tourette syndrome patients (mean age: 26.3 ± 9.4 years; mean education level 12.2 ± 3.4 years; male/female ratio: 20/5) participated in this study. Healthy

participants who took part in the fMRI study presented in chapter two (mean age: 25.7 ± 3.8 years; mean education level 15.6 ± 2.5 years; male/female ratio: 12/13; see chapter two for more details) represented here the control group (HC: healthy controls). All the participants were right-handed, as assessed by the Edinburgh handedness inventory (Oldfield 1971).
The majority of patients (n = 19) were on neuroleptics medication. Demographical data and medication molecules and dosages are reported in **Table A1** in the *Appendix*.
The study protocol was approved by the local Ethics Committee (IRCCS *San Raffaele* of Milan; Prot. SOA, 149/INT/2016), and informed written consent was obtained from all subjects according to the Helsinki Declaration (1964). All participants took part in the study after the nature of the procedure had been fully explained.

Neuropsychological and clinical evaluation

All patients were submitted to neuropsychological and psychopathological assessments and a detailed interview about the severity of their motoric symptoms.
The neuropsychological screening included the Mini-Mental State Examination (MMSE, Folstein et al. 1975), the Raven's Colored Progressive Matrices (Raven's Matrices, Raven et al. 1998), and the Frontal Assessment Battery (FAB, Dubois et al. 2000).
The psychopathological test battery included the Baratt Impulsivity Scale (BIS) for impulsivity (Fossati et al. 2001); the Yale-Brown Obsessive Compulsive Scale for obsessive-compulsive disorder (YBOCS, Goodman et al. 1989), the Beck Depression Inventory for depression assessment (BDI, Beck 1961) and the Adult ADHD Self-Report Scale for the attention deficit hyperactivity disorder (ASRS, Adler et al. 2006), as suggested by the European clinical guidelines for Tourette Syndrome and other tic disorders (Cath et al. 2011).
Motor symptoms' severity was assessed through the Yale Global Tic Severity Scale (YGTSS, Leckman et al. 1989) and the Premonitory Urge Tics Scale (PUTS, Woods et al. 2005).
Neuropsychological and clinical data are presented in **Table A1** in the *Appendix*.

Procedure

fMRI scans were acquired during the execution of a temporal judgment task. The experiment was performed in a single session in one day. It lasted approximately twelve minutes, depending on the individuals' reaction times. The task structure was event-related and interleaved.

Stimuli presentation was controlled by Cogent 2000 MATLAB Toolbox (MathWorks). Visual stimuli were presented using VisuaStim fiber-optic goggles (600x800 pixel resolution). Responses were recorded through response boxes placed under the participant's hands (Resonance Technology Inc., Northridge, CA, USA).
Before the experiment, subjects performed a training session composed of ten trials, when they received feedback on their performance.

Experimental task

Participants performed the same temporal judgment task previously employed in the fMRI and TMS experiments.
In brief, the task consisted of active and passive trials. Each trial started with the presentation of the picture of a turned-off lightbulb on the screen. For the active trials, the base of the bulb was colored in green. For the passive trials, the base was colored in red. Participants were instructed to press a button with their right index finger every time they saw a green lightbulb (active trials). They were invited to make the press at their own time. This was done to elicit a well-prepared, self-initiated button press, rather than an automatic movement as a reflex to the instruction. They were instructed to refrain from acting when the base of the lamp was colored in red (passive trials). In this case, the experimenter present inside the MRI room pressed participants' right index finger to induce a passive movement. In both conditions, the button press caused the illumination of the lamp. This could happen after 200, 400, or 600 milliseconds (ms) of delay. The feedback lasted 500ms. After 2000ms, participants then judged the perceived time interval between the button press and the illumination of the lamp. Judgments were reported by means of a visual scale at which they responded using a five-key response keypad placed under their left hand. They used their fingers to select one of five possible response options: 1ms, 200ms, 400ms, 600ms, and 800ms. The lowest and the highest response options were included to make it possible for the participants to underestimate and overestimate each presented time interval.
The task consisted of 60 trials, equally distributed between active and passive conditions, with ten trials for each delay. The inter-stimulus interval randomly varied between 1500ms and 2500ms. For a graphical representation of the task, see **Figure 1**.

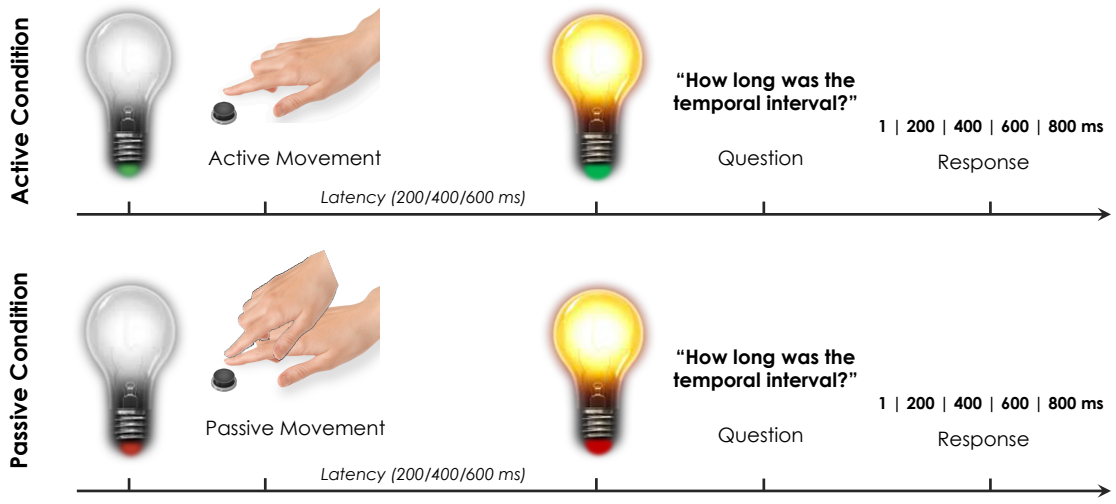


Figure 1 | Experimental task. Graphical illustration of an experimental trial for active and passive conditions. During the active trials, participants pressed a button with their right index finger at their own time after the presentation of the cue. In the passive trials, participants were instructed to stay still while an experimenter pressed their finger to produce a passive movement. In both conditions, the button press caused an action-consequence: the lightening of a lamp. The consequence was presented after a variable delay of 200, 400, or 600ms. Participants then judged the perceived time interval between their button press and the action-consequence.

Statistical analyses of the behavioral data

Behavioral data collected during the fMRI experiment were analyzed using the software SAS (Statistical Analysis System, version 9.4).

Four GTS patients were excluded from the behavioral analyses due to a technical problem in responses recording.

Linear mixed model

In line with the description of the intentional binding phenomenon (Haggard et al. 2002), the time compression represented the indirect measure of the sense of agency and was entered into the model as the dependent variable. It refers to the difference between the estimated and the real duration of the action-outcome delay. Thus, more negative time compression values stood for stronger degrees of the perceived sense of agency.

The independent variables of the model were the factors "Group" (HC/GTS), "Condition" (active/passive), and "Delay" (200/400/600ms). The model was tested by using linear mixed models with random intercept. Significant interactions were further explored by means of planned Bonferroni corrected post-hoc comparisons.

Before applying linear mixed models, data distribution was inspected using the skewness-kurtosis graph of Cullen and Frey (Cullen and Frey 1999), which provides the best fit for an unknown distribution according to skewness level and kurtosis. The present data had a distribution similar to the normal distribution.

Correlations with clinical data

To explore the possibility that time compression results were influenced by patients' clinical profile in terms of tics severity and psychopathological comorbidities, time compression data were correlated with the different clinical measures indicated in Table A1 by means of non-parametric correlation analyses.

Correlations with neuroleptic medication levels

To exclude the possibility that time compression results were influenced by patients' neuroleptic medication, time compression data were correlated with the neuroleptic dosages indicated in Table A1. Precisely, I first calculated the chlorpromazine equivalent scores (https://cpnp.org/guideline/essentials/antipsychotic-dose-equivalents). I then performed non-parametric correlation analyses between the time compression values and the chlorpromazine equivalent scores.

fMRI data acquisition and analysis

MRI scans were acquired using a 1.5 T Siemens *Avanto* scanner, equipped with gradient-echo echo-planar imaging (flip angle 90°, TE=40ms, TR=2000ms, FOV=250 mm and matrix=64x64). The overall number of the collected fMRI volumes varied from 269 to 292 volumes depending on the individual reaction's times. The first 15 volumes of the block corresponded to the instructions' presentation and were discarded from the analyses.

Pre-processing

After the image reconstruction, raw data visualization, and conversion from DICOM to the NIFTI format were performed with MRIcron (www.mricro.com) software. All the subsequent data analyses were performed in MATLAB R2014a (Mathworks Natick MA USA) using the

software Statistical Parametric Mapping (SPM12, Wellcome Department of Imaging Neuroscience, London, UK).

fMRI scans were realigned to the first image of the run to account for any head movement during the experiment. The structural T1 image was coregistered to the functional mean image to allow a more precise normalization. Then, the unified segmentation and nonlinear warping approach of SPM12 was applied to normalize structural and functional images to the MNI (Montreal Neurological Institute) template to permit group analyses of the data (Ashburner and Friston 1999, Friston et al. 1995). The data matrix was interpolated to produce 2 x 2 x 2 mm voxels. The stereotactically normalized scans were finally smoothed using a Gaussian filter of 10 x 10 x 10 mm to improve the signal-to-noise ratio and make the data suited for cluster-level correction for multiple comparisons (Flandin and Friston 2017).

The BOLD signal associated with each experimental condition was analyzed by a convolution with a canonical hemodynamic response function (HRF) (Worsley and Friston 1995). Global differences in the fMRI signal were removed from all voxels with proportional scaling. High-pass filtering (128s) was used to remove artifactual contributions to the fMRI signal.

Analysis of head motion parameters measured on the fMRI data

Considering the nature of the disorder, to exclude any possible confounding effect on the results of the motion artifacts during the fMRI scan, I compared the degree of absolute motion for healthy controls and GTS patients. Precisely, I compared the SPM realignment parameters between groups by means of multiple Mann–Whitney U tests (Shapiro Wilk's $p < 0.05$, for each parameter, in at least one of the groups).

First level fixed-effect analyses

A fixed-effect block-design analysis was performed for each subject to characterize the BOLD response associated with the task.

The brain activity between the appearance of the stimulus (the turned-off lightbulb) and the action consequence (the illumination of the lamp) was separately specified for each condition (active and passive conditions) and each action-outcome delay (200/400/600ms), for a total of six regressors.

The brain activity occurring between the appearance of the evaluation scale and the response was similarly specified, separately for each delay and condition (for a total of six regressors) and added to the statistical model as non-interest regressors.

The parameters obtained from the realignment procedure were added to the model to partial out the impact of motion artifacts on the estimates of the beta parameters.

In addition, I used the Artifact detection Toolbox (ART, Withfield-Gabrieli https://www.nitrc.org/projects/artifact_detect/). This toolbox identifies and discards from the analyses the scans containing excessive movement artifacts on the basis of the user's preferences. I set the thresholds at 2 mm scan-to-scan head movement and 9 standard deviation of scan-to-scan global signal intensity change following the toolbox guidelines. Experimental subjects that exhibited more than 20% outlier scans in the whole experimental run were excluded from the analyses. One HC participant was excluded from the analysis due to a strong artifact. No GTS included in the final sample exceeded these thresholds. The specific regressors generated by the ART toolbox were added as non-interest regressors in the analyses to exclude the outlier scans that exceeded the movement thresholds.

For each subject for each action-outcome delay, I then generated a contrast image of the comparison Active condition > Passive condition, for a total of three contrast images per subject.

Second level random effect analysis

The contrast images (Active condition > Passive condition) were entered in separate second level analyses, conforming to a random-effect approach (Holmes and Friston 1998).

Full factorial analysis

I first performed a full factorial analysis to test the following effects: (i) Main effects of the factor "Condition" (Active condition > Passive condition and Passive condition > Active condition), to highlight the brain activations of the task independently from the different groups and action-outcome delays. (ii) Conjunction effects of the comparisons Active condition > Passive condition and Passive condition > Active condition, to highlight the brain activations shared between the two groups independently from the different action-outcome delays. (iii) Interaction effect between the factor "Condition" (active/passive) and the factor "Delay"

(200/400/600msec) (iv) Interaction effect between the factor "Group" (GTS/HC), the factor "Condition" (active/passive) and the factor "Delay" (200/400/600msec).

Linear regression analyses

As for the healthy control group (Chapter two), I then performed three separate linear regression analyses, one for each action-outcome delay. These analyses were performed to test the hypothesis that the activity of some brain regions covaried with the measured sense of agency (time compression) in specific time-windows.

It is important to note that, because the contrast images used in this analysis contained the differential effect between active and passive trials (Active condition > Passive conditions at the specific action-outcome delay), differential Time compression values between active and passive trials (mean time compression in the Active condition – mean time compression in the Passive conditions at the specific action-outcome delay) was used as a regressor here. I then compared the correlation coefficients obtained for each group by using the Fisher r-to-z transformation.

All the results reported survive a correction for multiple comparisons: I used the nested-taxonomy strategy recommended by Friston et al. (Friston et al. 1996), including regional effects meeting either a cluster-wise or voxel-wise FWER correction. The voxel-wise threshold applied to the statistical maps before the cluster-wise correction was $p<0.001$ uncorrected, as recommended by Flandin and Friston (Flandin and Friston 2017). For clusters significant at the $p<0.05$ FWER-corrected level, I also report the other peaks at $p<0.001$.

Results

Behavioral Results

Time Compression data.

The results showed a significant effect of the factor "Condition" ($F(1, 2569)=7.49$, $p=0.006$), a significant effect of the factor "Latency" ($F(2, 2569)=4.97$, $p<0.007$), a significant "Latency*Group" interaction ($F(2, 2569)=29.68$, $p<0.0001$) and a significant "Condition*Latency*Group" interaction ($F(4, 2569)=3.76$, $p=0.005$). The factor "Group" ($F(1, 2569)=0.12$, $p=0.73$), and the "Condition*Group" interaction were not significant ($F(1, 2569)=0.58$, $p=0.45$).

The "Condition*Latency*Group" interaction was then explored with planned post-hoc comparisons. As seen in chapter two, healthy controls showed significantly stronger time compression values in the active than passive trials at 200ms of delay. The same comparison was not significant for the Gilles de la Tourette patients' group.

At longer delays, time compression values were not significantly different between active and passive conditions, in any group. For more details, please see **Table 1** and **Figure 2**.

Table 1 | Planned post-hoc comparisons. Comparisons between time compression values in the active and passive conditions at different action-outcome delays in Healthy Controls (HC) and Gilles de la Tourette syndrome patients (GTS). For each comparison, I reported the mean difference, the standard error (SE), the value of the statistic, the corresponding degrees of freedom (df), and the associated Bonferroni-corrected p-value. Asterisks indicate significant results at $p < 0.05$ Bonferroni corrected.

Comparison											
Condition	**Delay**	**Modality**		**Condition**	**Delay**	**Modality**	**Difference**	**SE**	**t test**	**df**	**Bonferroni-corrected p**
Passive	200	HC	-	Active	200	HC	65.49	18.3	3.58	2569	0.02*
Passive	400	HC	-	Active	400	HC	32.77	18.1	1.81	2569	0.2
Passive	600	HC	-	Active	600	HC	-18.02	17.9	-1.01	2569	p>.99
Passive	200	GTS	-	Active	200	GTS	46.32	19.3	2.40	2569	0.051
Passive	400	GTS	-	Active	400	GTS	-7.55	19.4	-0.39	2569	p>.99
Passive	600	GTS	-	Active	600	GTS	6.57	19.3	0.34	2569	p>.99

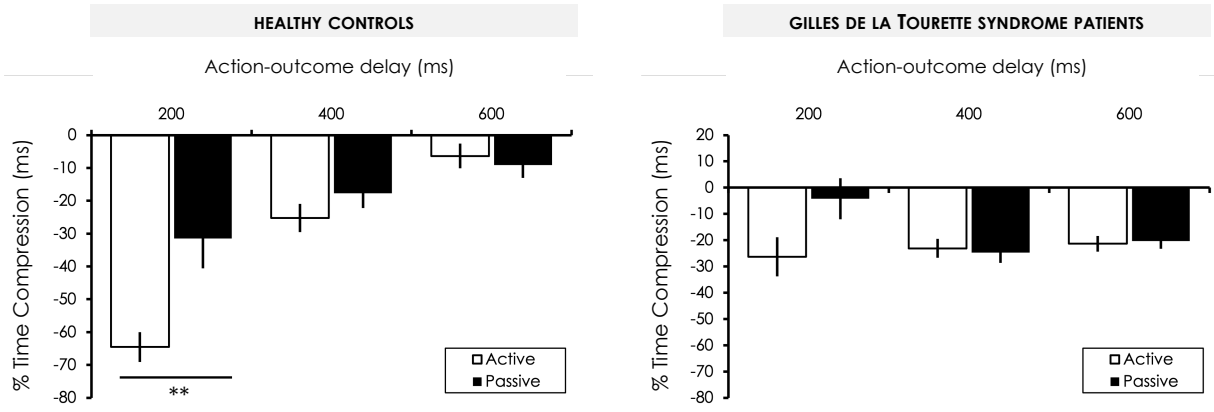


Figure 2 | Behavioral results showing the time compression values for the active and passive conditions recorded at 200, 400 and 600ms of action-outcome delay. Error bars = standard error; asterisks indicate significant results at $p < 0.05$ Bonferroni corrected. Please note that the results are reported here as a percentage of the compression with respect to the action-outcome delay (for visualization only)

Correlation between clinical data and behavioral results

The results showed a significant relationship between the motor symptoms' severity (measured with the YGTSS scale, subscale motor tics) and time compression values in the active condition at 200ms of delay. In particular, lower time compression data were associated with more severe motoric impairment levels (Spearman's Rho=0.46; one-tailed p-value=0.028). See **Figure 3**.

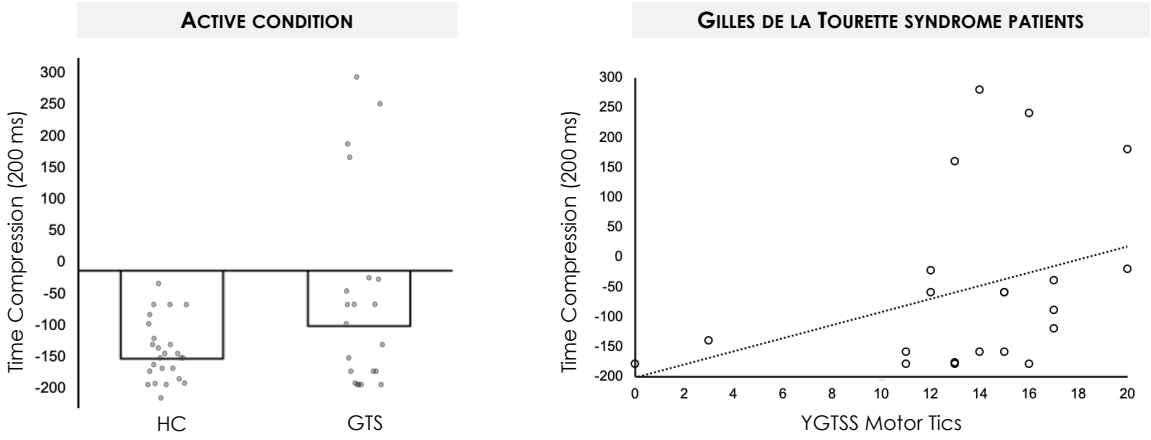


Figure 3 | On the left time compression values at 200ms of delay for healthy controls (HC) and Gilles de la Tourette syndrome patients (GTS) in the active condition. On the right, correlation analysis between the time compression values in the active condition at 200ms and the severity of the motor symptoms (measured with the YGTSS scale – subscale motor tics) in Gilles de la Tourette syndrome patients.

No significant correlation was shown between the time compression data at 200ms in the active condition and the Baratt Impulsivity Scale (BIS) for impulsivity (Fossati et al. 2001), the Yale-Brown Obsessive Compulsive Scale for obsessive-compulsive disorder (YBOCS, Goodman et al. 1989), the Beck Depression Inventory for depression assessment (BDI, Beck 1961) and the Adult ADHD Self-Report Scale for the attention deficit hyperactivity disorder (ASRS, Adler et al. 2006) (highest Spearman's Rho=-0.3, lowest p-value=0.18).

Correlations with neuroleptic medication levels

No significant correlation between time compression data and neuroleptic medication scores was displayed (highest Spearman's rho=0.168, lowest p-value=0.466).

fMRI results

Analysis of head motion parameters during the fMRI session

There were no significant between-group differences for any of the fMRI realignment parameters. Please, see **Table A2** in the *Appendix*.

Full factorial analysis

Active condition > Passive condition

The results showed significant activations in a large bilateral brain network, including prefrontal, premotor, motor, somatosensory regions and cerebellum. Further activations were found in the occipital cortices. Please, see **Table A3** in the *Appendix*.

Passive condition > Active condition

The results showed significant bilaterally activations in the secondary somatosensory areas and in the middle temporal gyrus. Please see **Table A4** in the *Appendix*.

Active condition > Passive condition (Conjunction analysis: HC ∩ GTS)

The results showed similar activations in the left motor/premotor network and in the left cerebellum in both HC and GTS participants. Please see **Table A5** in the *Appendix*.

Passive condition > Active condition (Conjunction analysis: HC ∩ GTS)

No region displayed a significant effect.

Main effect of the factor Group Active condition > Passive condition (HC > GTS or GTS > HC)

No region displayed a significant effect.

Passive condition > Active condition (HC > GTS or GTS > HC)

No region displayed a significant effect.

Interaction effect between "Condition" (active/passive) and "Delay" (200/400/600ms).

No region displayed a significant effect.

Interaction effect between "Group" (GTS/HC), "Condition" (active/passive) and "Delay" (200/400/600ms).

No region displayed a significant effect.

Linear regression analyses

Time compression values (active > passive trials) at 200ms of delay

As reported in Chapter two, HC showed a significant correlation between the differential time compression values (mean time compression in the Active condition – mean time compression in the Passive conditions at 200ms) and the BOLD activity (Active condition > Passive conditions at the 200ms) of a wide brain network, including the left pre-supplementary motor area (pre-SMA), the left precentral gyrus (Brodmann area 6), the superior parietal lobule (Brodmann area 40), the postcentral gyrus (Brodmann area 2) the insular cortex, the cerebellum bilaterally, the left hippocampus and the bilateral superior frontal gyrus (Brodmann areas 6 and 8), the bilateral thalamus and the left pallidus (see Chapter two). The same correlation was no longer significant in GTS patients. No brain regions significantly correlated with the magnitude of the intentional binding phenomenon at 200ms of delay in GTS patients.

The Fisher r-to-z transformation showed that the correlation coefficients (r) - indicating the strength of the association between the BOLD activity of the key regions of the sense of agency

network in HC and the individually measured time compression values - were significantly higher in HC than the same coefficients calculated for the GTS group (pre-SMA: r HC=-0.73, r GTS=0.0003, z=-2.89, p-value=0.004. Parietal site: r HC=-0.68, r GTS=0.00009, z=-2.58, p-value=0.01. Cerebellum left: r HC=-0.65, r GTS=0.0008, z=-2.42, p-value=0.01. Cerebellum right: r HC=-0.73, r GTS=0.0003, z=-2.89, p-value=0.004). For a graphical representation of the results, please see **Figure 4**.

Finally, in order to check whether the abnormal activation of the agency network in the GTS was related to the neuroleptic's medication dosage, I correlated the activity of the key regions of the sense of agency network with the chlorpromazine equivalent scores. These regions' activity was not significantly associated with the drug dosage (highest Spearman's rho=0.281, lowest p-value=0. 23).

Time compression (active > passive trials) at 400ms and 600ms of delay

No region displayed a significant correlation with the differential time compression values at 400ms and 600ms of delay, nor in GTS neither in HC participants.

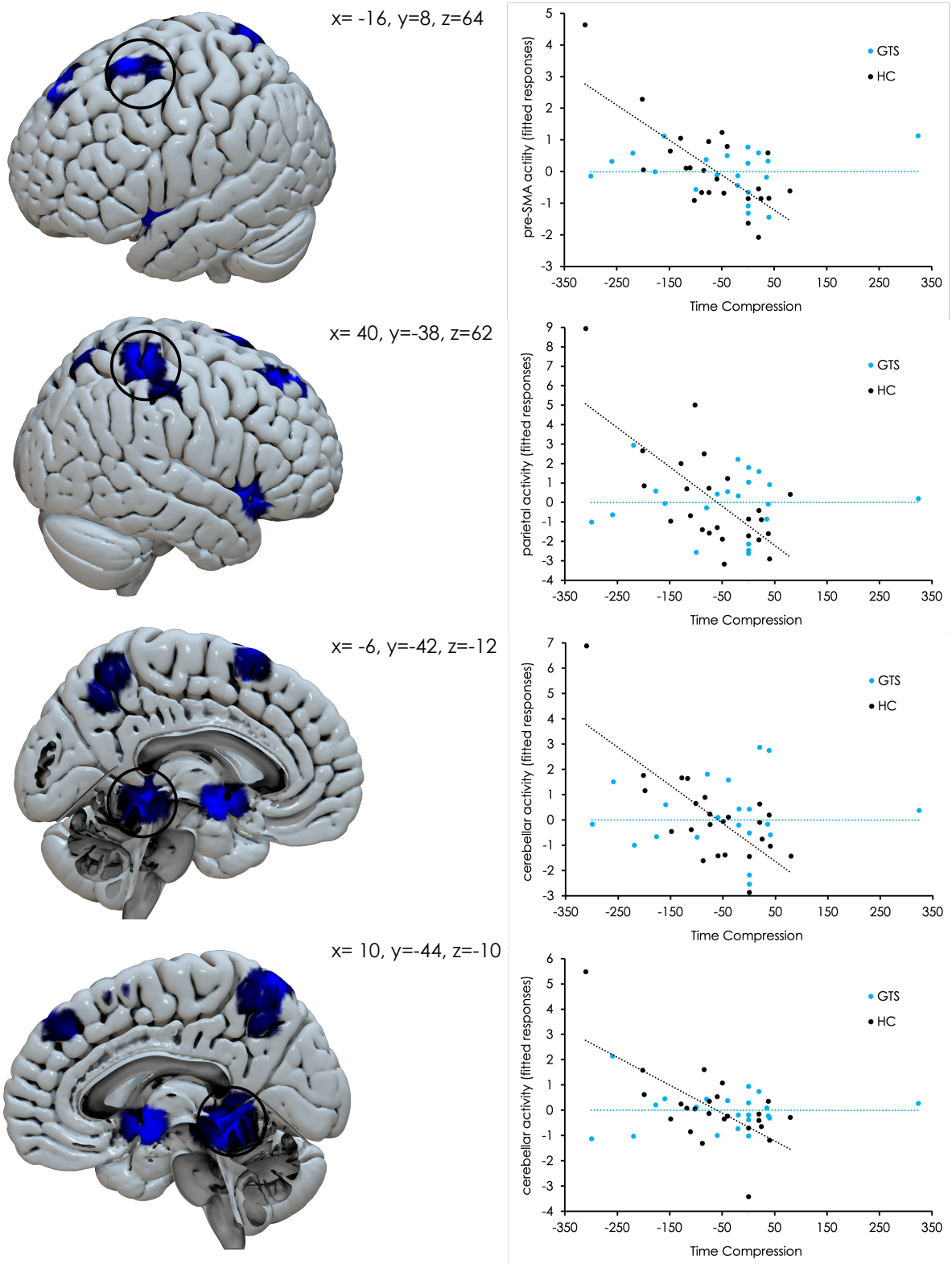


Figure 4 | fMRI Results. Linear regression analysis between the BOLD activity (fitted responses in the local maxima for HC) and the differential time compression values (active trials – passive trials) when the action-outcome delay was 200ms and a significant intentional binding was observed in HC (but not in GTS).

Discussion

In this chapter, I tested the hypothesis that the sense of agency might be impaired, at the behavioral and at the brain activation level, in Gilles de la Tourette Syndrome (GTS), a movement disorder characterized by the presence of unwanted movements called tics.

I explored the behavioral manifestations and the neural correlates of a distortion in time perception following voluntary action, which is taken as a putative implicit marker of the sense of agency. This distortion in time perception is called "intentional binding" (Haggard et al. 2002) and refers to a perceived compression between the time of voluntary action and the time of the following sensory effect. I measured this intentional binding effect through a temporal judgment task in which participants estimated the time interval between a button press and a subsequent visual event that followed the action by 200, 400, or 600ms of delay.

Behavioral results showed an abnormal sense of agency in GTS patients, who, as a group, did not show the expected intentional binding effect. Precisely, unlike the healthy subjects, GTS patients did not report shorter interval estimations in the active condition compared to the passive condition, at any action-outcome delay.

This evidence may be interpreted as a sign of a reduced sense of agency in Gilles de la Tourette's Syndrome patients. Precisely, an absent intentional binding effect following voluntary actions may suggest that GTS patients do not experience agency in circumstances where they should, and they might treat as non-self-generated action consequences that they actually produced.

Importantly, the binding reduction in Gilles de la Tourette syndrome described here was related to the severity of the disease in terms of motoric symptoms: the greater the severity of motor tics, as measured by the Yale Global Tic Severity Scale (YGTSS) scale, the more reduced the time compression for intentional acts. It follows that more serious the motor impairment seems to be related to greater difficulties in attributing self-generated effects to themselves. Conversely, GTS patients with less acute motor symptomatology seem less prone to sense of agency disturbances. Importantly, similar correlation analyses between time compression values for intentional acts and the Baratt Impulsivity Scale (BIS) for impulsivity (Fossati et al. 2001), the Yale-Brown Obsessive Compulsive Scale for obsessive-compulsive disorder (YBOCS, Goodman et al. 1989), the Beck Depression Inventory for depression assessment (BDI, Beck 1961), and the Adult ADHD Self-Report Scale for the attention deficit hyperactivity

disorder (ASRS, Adler et al. 2006) were not significant. These results then ruled out the possibility that disturbances of the sense of agency may result from other characteristic features of the Gilles de la Tourette syndrome. Conversely, they highlighted the undeniable link between the abnormal sense of agency in GTS patients and the functioning of the motor system.

On the one hand, these findings have important implications also for the understanding of the sense of agency. In particular, they support the view that the brain mechanisms that give rise to the sense of agency are anchored to the functioning of the motor system (Frith et al. 2000, Wolpert et al. 1995, Wolpert and Ghahramani 2000). In other words, the conscious experience of action seems to be directly related to the underlying neural motor processes that cause the action itself. Crucially, an abnormal sense of agency in GTS patients was also evident from the fMRI data, which differed substantially between groups. GTS patients did not show any noticeable activity of the brain areas that showed a significant correlation with the magnitude of the intentional binding phenomenon in healthy subjects. Among them, the pre-SMA – a key structure for preparing and initiating voluntary actions (Cunnington et al. 2003, Zapparoli et al. 2018). – has proven to be a key region in the sense of agency generation, showing not only a significant correlation with the intentional binding effect (study one, chapter two) but also a causal role in its generation (study two, chapter three). Therefore, these findings complete the circle of a conceptual validation of the implicit sense of agency as a phenomenon anchored to the functioning of the motor system, showing a specific association between disturbances of the sense of agency in Gilles de la Tourette syndrome, the motoric symptoms and the activity of the premotor regions involved in voluntary motor control.

On the other hand, these results draw some important considerations about the syndrome. Notably, the mechanisms underlying tic expression in Gilles de la Tourette syndrome patients are still poorly understood. However, recent fMRI studies highlighted specific cortico-striatal mechanisms, including the supplementary motor area (SMA), the premotor cortex, the insula, the sensorimotor cortex (S1 and M1), the putamen, the globus pallidus, and the thalamus (Zapparoli, Porta and Paulesu 2015, Bohlhalter et al. 2006, Neuner et al. 2014) in various aspects of tic generation and suppression. In particular, during tic generation, the cortical activity in SMA seems to precede the activity of the basal ganglia, suggesting that SMA hyperactivity induces a cascade of aberrant activity through cortico-striato-thalamo-cortical (CSTC) circuits via the putamen (Ganos, Roessner and Münchau 2013). Recently, Rae et al. (2019) proposed an intriguing explanation of the Gilles de la Tourette syndrome, based on two

aberrant processes. First, the aforementioned overactivity of the SMA (but not pre-SMA) would lead to increased glutamatergic (excitatory) inputs to the putamen. Second, the reduced density of GABAergic interneurons in the putamen would cause an aberrant synaptic integration. This results in thalamic disinhibition and release of signals for movement to M1, without the direct involvement of the pre-SMA in the process of generating the movement (Rae, Critchley and Seth 2019). The motor system would thus generate movements without the corresponding generation of sensorimotor predictions in the pre-SMA, needed for a normal experience of agency. Consequently, the motor system would trigger the hyperproduction of unwanted movements that are actually perceived as outside the agent's control. Since the induced movement is inconsistent with the patient's determined intentions and goals, this would determine a concomitant abnormal experience of agency or "alienness" for the generated action, which would justify the subjective perception of the aberrant movements as tics. In line with this hypothesis, not only Gilles de la Tourette syndrome did not show an intentional binding effect following voluntary movements, but also they did not show any correlation between the putative marker of the sense of agency and the activity of brain areas, including the pre-SMA, that correlate with the intentional binding effect in the healthy controls. It follows that, although much of this theory on the neuropathology of Gilles de la Tourette syndrome is still speculative (Rae et al. 2019), the present data support this hypothesis. Beyond the present experimental evidence regarding disturbances of the sense of agency in GTS, further works on the neuroanatomy relating to tics' core symptoms, premonitory sensations, and tic suppression are now the key directions for future investigation.

Limitations

It is worth noting that the present study suffers from some limitations. For example, at the moment of the fMRI examination, GTS patients were under treatment, similarly to what was reported in several previous imaging studies (for a review, see Martino, Ganos and Worbe 2018, Table 2, or Kim et al. 2019). The co-occurrence of medication limits the possibility of making firm conclusions about the disturbances of the sense of agency in unmedicated GTS patients. However, the present findings remain relevant for a substantial proportion of adult GTS patients from the real world, the medicated ones. According to some estimates, these can be more than 20% of the adult GTS population (Burd et al. 2001).

Second, the GTS patients included in the present study were sufficiently ill to need medication, but they still had manifestations compatible with the fMRI examination. The more severe patients' sense of agency physiology remains to be explored, possibly with techniques that have fewer practical constraints than fMRI.

Conclusions and implications

In this study, I showed an abnormal sense of agency in GTS patients, who, as a group, did not show the expected intentional binding effect. The binding reduction was related to the severity of the disease in terms of motoric symptoms as measured by the YGTSS scale. Moreover, GTS patients did not show any noticeable activity of the brain areas that showed a significant correlation with the magnitude of the intentional binding phenomenon in healthy subjects. Taken together, these findings complete the circle of a conceptual validation of the implicit sense of agency as a phenomenon anchored to the functioning of the motor system. Moreover, they provide new hints about the functional characteristics of the syndrome, supporting the view of Gilles de la Tourette syndrome as a movement disorder affecting the conscious experience of action.

Importantly, an aberrant experience of agency may have important implications for patients' quality of life. The ubiquity of the sense of agency in human life is undeniable. It is involved in any exchange between the agent and the environment. It represents the mechanism by which the self-generated stimuli can be distinguished from external-generated sensations. It also contributes to people's self-awareness, allowing them to feel unique and different from others based on their behavior. In addition, it represents the basis for developing a feeling of responsibility for the consequences of the generated actions, but also an important cue for attributing legal liability (Frith 2014, Haggard 2017). In principle, someone who lacks a sense of agency for an action cannot be held criminally responsible for that action. However, lack of agency is difficult to attest objectively, and there is an obvious social risk associated with any legal immunity. It is therefore clear that aberrant experiences of agency may have a major impact on patients' life. It is thus now incumbent on agency researchers to use findings from patients with disorders of the sense of agency to develop interventions aimed at restoring them.

Appendix

Table A1 | Neuropsychological, clinical data and medication dosage.

Patients' evaluation

#	*Neuropsychological data*						*Psychopathological data*						*Motor severity assessment*				*Neuroleptic treatment*
	MMSE		*FAB*		*Raven*		*BIS-11*	*Y-BOCS*	*Beck*	*Conners*	*STAI-X-1*	*STAI-X-2*	*PUTS*	*YGTSS*			
	Raw	*Corr*	*Raw*	*Corr*	*Raw*	*Corr*								*Moto*	*Fon*	*Soc*	
1	29	28.19	18	18	31	30.5	65	24	13	2	31	40	21	13	11	20	Risperidone (2 mg)
2	24	**22.59**	16	14.9	18	16	77	19	22	2	62	56	26	21	21	50	None
3	30	30	18	18	35	32.5	58	15	12	2	41	50	29	15	5	20	None
4	30	30	17	15.9	28	26	62	2	10	0	55	53	34	20	17	20	Aripiprazole (22.5 mg); Pimozide (4 mg)
5	30	30	18	18	35	32.5	58	13	1	2	31	54	24	17	7	30	Aripiprazole (7.5 mg); Pimozide (2 mg)
6	30	30	18	18	35	32.5	68	16	2	2	45	43	25	11	5	40	Aripiprazole (15 mg)
7	30	30	17	15.6	34	31.5	84	13	7	3	27	43	21	20	14	20	Pimozide (2 mg)
8	26	24.59	16	14.5	35	32.5	71	16	8	4	26	44	32	13	5	0	Quetiapine (50 mg)
9	29	27.59	13	**12.1**	30	29	55	19	7	4	34	32	28	6	7	20	Pimozide (4 mg)
10	29	27.59	15	13.5	22	19.5	86	16	5	5	47	36	26	12	11	0	Haloperidol (2 mg); Aripiprazole (15 mg)
11	28	27.19	16	15.5	24	24	63	13	4	1	31	45	19	11	10	30	Aripiprazole (30 mg); Pimozide (2 mg)
12	30	30	18	18	36	36	57	20	13	0	41	51	27	14	0	20	Aripiprazole (30 mg)
13	27	25.59	16	14.5	30	28	48	17	2	0	53	40	25	12	13	20	Aripiprazole (15 mg)
14	29	28.97	14	13.9	22	23.5	67	11	0	2	30	25	27	8	7	40	Aripiprazole (30 mg)

15	30	30	18	18	35	32.5	61	20	5	4	37	45	36	15	6	20	Pimozide (4 mg)
16	29	27.59	18	18	30	26.25	70	18	17	1	35	47	34	16	6	40	Aripiprazole (15 mg)
17	30	30	16	15.3	32	32	76	20	7	4	29	33	21	14	0	20	Aripiprazole (22.5 mg); Pimozide (4 mg)
18	30	30	18	18	32	32	70	17	11	4	33	50	10	0	0	50	Aripiprazole (15 mg)
19	30	30	17	15.5	36	36	74	10	7	4	34	52	28	17	0	20	Pimozide (4 mg)
20	29	28.19	16	15.3	34	34	60	0	0	0	24	23	14	3	4	0	Aripiprazole (22.5 mg)
21	30	30	17	15.3	28	24.5	86	12	11	4	39	50	29	15	12	30	None
22	29	27.89	18	18	30	29.5	68	18	8	2	41	39	36	17	18	20	None
23	27	26.62	16	15.8	28	26.75	67	10	0	1	37	39	22	11	3	0	Pimozide (4 mg)
24	30	30	18	18	34	30	70	19	20	4	59	41	34	16	11	30	None
25	30	30	18	18	29	25.25	51	21	14	2	50	69	33	11	13	40	None
Mean	**29**	**30**	**16.8**	**18**	**30.5**	**29.4**	**66.9**	**15.2**	**8.2**	**2.4**	**38.9**	**44**	**26.4**	**13.1**	**8.2**	**24**	
SD	**1.5**	**0**	**1.4**	**0**	**4.9**	**5.9**	**10.1**	**5.6**	**6.1**	**1.6**	**10.5**	**10**	**6.6**	**5**	**5.8**	**14.4**	

Table A2 | Head Movement parameters: comparison between groups.

	Movement parameters			Comparison		
		HC	GTS	Mann-Whitney U test	df	Bonferroni-corrected p-value
Translation - x	Mean	0.004	0.071	U=223	43	p>0.99
	SD	0.365	0.300			
Translation - y	Mean	0.041	0.073	U=226	43	p>0.99
	SD	0.140	0.245			
Translation - z	Mean	-0.061	0.096	U=235	43	p>0.99
	SD	0.430	0.349			
Rotation - x	Mean	0.000	0.004	U=139	43	p>0.99
	SD	0.004	0.009			
Rotation - y	Mean	-0.002	0.000	U=201	43	p>0.99
	SD	0.003	0.006			
Rotation - y	Mean	-0.002	-0.001	U=223	43	p>0.99
	SD	0.004	0.006			

Table A3 | Results of the comparison between Active > Passive trials, independently from the different action-outcome delay and the group. *p<0.05 FWER corrected (voxel level).

Brain regions (BA)	MNI coordinates							
	Left hemisphere				Right hemisphere			
	x	y	z	Z-score	x	y	z	Z-score
Rolandic opercular gyrus	--	--	--	--	44	8	14	3.6
Inf. frontal op. gyrus	-50	14	0	4.1	44	12	16	3.5
	-52	18	22	3.6	44	10	22	3.2
Inf. frontal op. gyrus (44)	-46	8	26	3.6	52	10	32	4.1
	-46	4	28	3.5	40	12	12	3.3
Inf. frontal tri. gyrus (45)	-42	36	20	4.3	--	--	--	--
	-46	28	20	3.8	--	--	--	--
	-52	22	20	3.6	--	--	--	--
	-36	44	14	3.3	--	--	--	--
	-42	34	8	3.5	--	--	--	--
Mid. frontal gyrus (46)	-36	52	16	3.5	38	44	24	4.7*
	--	--	--	--	38	38	30	4.4
	--	--	--	--	30	52	20	4.1
Mid. frontal gyrus (6)	--	--	--	--	36	4	60	3.8
	--	--	--	--	36	-4	62	3.2
Mid. cingulum (24/32)	--	--	--	--	0	12	44	5.7*
	--	--	--	--	8	12	40	5.4*

Sup. frontal gyrus (6)	--	--	--	--	36	-4	62	3.2
Precentral gyrus (6)	--	--	--	--	38	-16	64	3.6
	--	--	--	--	42	-10	58	3.3
	--	--	--	--	48	-8	50	3.2
SMA (6)	-2	-14	54	5.2*	0	-10	52	5.3*
	-2	2	50	4.6	4	0	58	4.3
Precentral gyrus (4)	-34	-22	60	7.3*	32	-20	48	4.0
	--	--	--	--	32	-16	44	4.0
	--	--	--	--	36	-14	42	3.8
	--	--	--	--	40	-16	54	3.8
Postcentral gyrus (2)	--	--	--	--	46	-28	42	3.8
Postcentral gyrus (3)	--	--	--	--	38	-20	46	3.9
					36	-20	50	4.0
	--	--	--	--	42	-24	44	3.6
Insula	--	--	--	--	38	24	0	4.1
	--	--	--	--	40	20	0	4.0
	--	--	--	--	38	14	4	4.0
	--	--	--	--	46	12	0	4.0
Sup. parietal gyrus (7)	-14	-68	48	3.8	24	-66	48	4.8*
	-24	-64	38	3.9	--	--	--	--
	-20	-62	48	3.7	--	--	--	--
	-22	-68	46	3.5	--	--	--	--
Sup. temporal pole	-48	10	-2	4.0	--	--	--	--
Supramarginal gyrus (40)	--	--	--	--	46	-32	44	3.8
	--	--	--	--	48	-38	44	3.8
	--	--	--	--	52	-40	42	3.3
Fusiform gyrus (19)	-34	-66	-12	4.4	--	--	--	--
Sup. occipital gyrus (19)	-24	-64	30	3.3	24	-82	32	3.6
Mid. occipital gyrus (19/18)	-32	-82	16	4.9*	30	-88	6	4.8*
	-40	-78	0	4.7*	28	-70	34	3.6
	-40	-80	4	4.6	--	--	--	--
	-32	-90	16	4.4	--	--	--	--
Inf. occipital gyrus (19)	-36	-68	-8	4.4	32	-80	-6	4.6
Lingual gyrus (17)	-2	-72	6	4.5	--	--	--	--
Calcarine fissure (17)	-10	-84	12	4.4	--	--	--	--
Cerebellum_6	-18	-56	-16	5.7*	28	-52	-20	5.4*
	-22	-68	-18	4.5	36	-64	-24	4.5
	--	--	--	--	32	-42	-28	4.5
Vermis	--	--	--	--	4	-70	-14	4.9*

Table A4 | Results of the comparison between Passive > Active trials, independently from the different action-outcome delay and the group. *p<0.05 FWER corrected (voxel level).

Brain regions (BA)	MNI coordinates							
	Left hemisphere				Right hemisphere			
	x	y	x	Z-score	x	y	x	Z-score
Rolandic opercular gyrus (SII)	-46	-28	20	5.2*	52	-28	24	4.6*
Supramarginal gyrus	-58	-26	22	3.7	--	--	--	--
	-58	-30	24	3.7	--	--	--	--
Mid. temporal gyrus (37)	-46	-64	14	5.0*	48	-60	14	4.4
	-48	-60	14	4.9*	52	-60	12	4.4
	-58	-46	10	3.8	54	-60	24	3.7
Mid. temporal gyrus (39)	--	--	--	--	52	-66	24	3.7

Table A5 | Results of the conjunction analysis between HC and GTS of the comparison Active > Passive trials, independently from the different action-outcome delay.

Brain regions (BA)	MNI coordinates							
	Left hemisphere				Right hemisphere			
	x	y	z	Z-score	x	y	z	Z-score
Precentral Gyrus (6)	-26	-24	58	4.1				
	-28	-24	64	4.0				
	-26	-22	68	4.0				
Precentral Gyrus (4)	-40	-22	56	3.3				
Cerebellum_4_5	-12	-54	-14	3.9				
	-20	-52	-20	3.6				
Cerebellum_6	-14	-58	-16	3.9				
	-22	-56	-18	3.8				
	-26	-54	-20	3.7				

Chapter 6

General discussion

In this thesis, I have studied the human sense of agency, the compelling feeling of control that accompanies and characterizes voluntary actions.

In the last two decades, a growing body of neuroscientific literature has tried to elucidate how the sense of agency is generated in the brain. It has been suggested that the sense of agency is not a transcendental feature of human nature but the result of the activity of specific brain areas, including the insula, the parietal lobules and the frontal middle line areas (for a review, please see Haggard 2017; for a meta-analysis of the brain imaging studies, please see the chapter one of this thesis). Despite such progress, however, the results of previous studies are often inconsistent, incomplete, or contentious. As aforementioned, one major limit regards the methodological problem of designing experimental paradigms able to capture the sense of agency in an ecologically relevant state in a research environment. Several neuroimaging studies adopted the so-called "explicit measures" of the sense of agency, asking participants to overtly report their agentic experience of action. Explicit measures are undoubtedly intuitive, but they can be vulnerable to consistent cognitive biases typical of self-report measures (see, for example Wegner and Wheatley 1999). Moreover, it has been discussed that in our everyday life, we usually feel an implicit sense of agency, running in the background of our mental life, which is not based on explicit judgments (Kühn et al. 2013). Given these limits, it has been

recommended that the sense of agency should be studied by implicit measures, instead (Haggard 2017). A major one is the intentional binding effect (Haggard et al. 2002, Moore and Obhi 2012). Since its seminal introduction, this bias in the perceived time of voluntary actions and their outcomes has become one of the most widely used implicit markers of the sense of agency. However, the investigation on this putative marker of the sense of agency is still incomplete. Only one neuroimaging study explored the neural correlates of the intentional binding applying a small volume correction in a very circumscribed area (Kühn et al. 2013), and non-invasive brain stimulation studies are inconsistent for both the target stimulated area and the timing of the stimulation (Cavazzana et al. 2015, Khalighinejad and Haggard 2015, Moore et al. 2010a).

In this thesis, I carried out a series of experiments using different behavioral tasks, brain imaging, and stimulation techniques to explore the neurofunctional bases of the sense of agency by taking advantage of the intentional binding in a coherent experimental setting across studies. Below I will summarize the main findings from each study.

In **study one** (chapter two), I explored the subjective experience of agency and its neural correlates, using the intentional binding effect as a marker for the sense of agency in an fMRI setting. I found that the perceived time interval between the action and its subsequent effect was shorter than the same interval following a physically comparable passive movement, replicating the previously reported intentional binding effect (Haggard et al. 2002). However, the binding effect was strongly different based on the time delay between the action and its sensory effect: while I observed a significant intentional binding effect at 200ms of delay, the same effect was greatly reduced at 400ms and absent at 600ms. Crucially, at 200ms of delay, the magnitude of the intentional binding effect was also mirrored by meaningful brain activity in a broad network, including the bilateral insular cortex, precuneus and cerebellum, the left pre-SMA, the left hippocampus, the right superior frontal gyrus, and the right inferior parietal lobule. This experiment represents an important foundation study needed to better characterize the subjective experience of agency, and its neurobiological bases. In particular, it shows that the sense of agency is the result of the activity of specific brain areas, and represents the prerequisite to then explore the sense of agency system from a functional point of view.

In **study two** (chapter three), I then extended the investigation of the neural correlates of the sense of agency by measuring the effects of locally interfering with the brain activity of the identified agency network on the sense of agency experience. Two target brain areas were stimulated with repetitive transcranial magnetic stimulation (rTMS): the left pre-supplementary motor area (pre-SMA) and the right inferior parietal lobule, identified using the local maxima of the previous fMRI findings. I explore the effect of two different timing of stimulation: before the action execution, time-locked to the trial instruction's presentation (*experiment 1*, chapter two), and after the action execution, time-locked to the appreciation of the action consequences (*experiment 2*, chapter two). I found that when rTMS was applied over the pre-SMA before the action execution, participants showed the temporal marker of agency even for longer delays, expanding the time-window for the intentional binding effect from 200ms of delay up to 400ms. The effect was specific for the target pre-SMA area and the timing of the stimulation. The stimulation of the same area after the motor execution did not produce any significant change with respect to the baseline. At the same time, modulating the parietal site activity with rTMS did not significantly affect the binding effect in any timing of stimulation. This study shows that the pre-SMA not only contributes to the sense of agency, but it has a *causal* role in its generation. Moreover, the timing of its contribution suggests a possible *predictive* role of the pre-SMA in the sense of agency generation.

In **study three** (chapter four), I then focused on the role of the action-outcome in generating a sense of agency. In particular, I assessed the experience of agency, and its neural correlates, for action consequences in a different sensory modality compared to that tested in the previous fMRI study. Specifically, while I used visual feedback before, the sensory effect produced by the voluntary action in this task was an auditory tone. I showed distinctive time-windows for the sense of agency manifestations for the different sensory modalities of the outcome. While in the previous fMRI study, I reported an intentional binding effect in the condition of a stringent 200ms temporal contiguity between the action and the visual outcome, I observed here a sizeable time compression when the auditory outcome followed the action by 400ms. This difference in the behavioral manifestation of the sense of agency was mirrored by similar peculiarities at the neural level. While in the previous fMRI study, I reported a significant correlation between pre-SMA activity and intentional binding effect at 200ms of delay, the same correlation was significant only at 400ms of delay between the voluntary action and the

subsequent auditory tone. On the one hand, this study shows that the subjective experience of agency is modulated by the distinctive features of the outcome, showing different patterns of manifestation based on the specific action effect. On the other hand, attributing diverse consequences of self-generated movements to our actions seems to be based on similar mechanisms, and that these mechanisms are strongly related to the functioning of the pre-SMA.

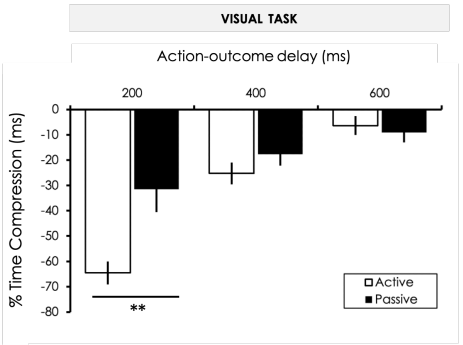
In **study four** (chapter five), I expanded my investigation to a clinical population affected by Gilles de la Tourette syndrome (GTS), a movement disorder characterized by unwanted movements called tics. I found an abnormal sense of agency in Gilles de la Tourette patients, who, as a group, did not show the expected intentional binding effect. Importantly, the binding reduction was related to the severity of the disease in terms of motoric symptoms: the greater the severity of motor tics, as measured by the Yale Global Tic Severity Scale (YGTSS), the more reduced the time compression for intentional acts. Abnormalities in the sense of agency system were also evident from the fMRI patterns of activation of the brain regions typically involved in the sense of agency. GTS patients did not show any noticeable activity of the brain areas that showed a significant correlation with the magnitude of the intentional binding phenomenon in healthy subjects, probably reflecting an overwhelmed sensorimotor system. This study shows that disturbances of the sense of agency may be related to specific dysfunction in the sensorimotor system. Moreover, it provides new hints about the functional characteristics of the syndrome, supporting the view of Gilles de la Tourette syndrome as a movement disorder affecting the conscious experience of action.

In summary, the present results enhance our knowledge about the subjective experience of agency, and its neural correlates, by showing a link between the sense of agency and the medial premotor cortex, particularly the pre-SMA. The association between the sense of agency and the pre-SMA is compelling and discloses the motoric nature of this elusive feeling of control that accompanies and characterizes voluntary actions. The results on Gilles de la Tourette syndrome patients complete the circle of a conceptual validation of the sense of agency as a phenomenon anchored to the functioning of the motor system. Moreover, they provide new implications for understanding and treating disorders of the sense of agency.
For a synopsis of the main results of this thesis, please see **Figure 1**.

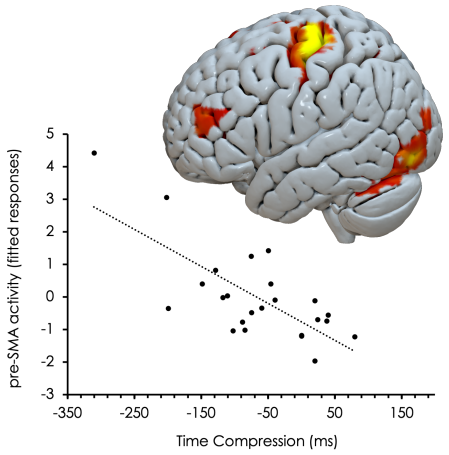
Study one, chapter two

Aim: Exploring the subjective experience of agency, and its neurofunctional correlates, using the intentional binding effect as a marker for the sense of agency, in an fMRI setting.

Behavioral Results: Participants reported an intentional binding effect at 200ms of delay between a voluntary action and a subsequent visual effect.



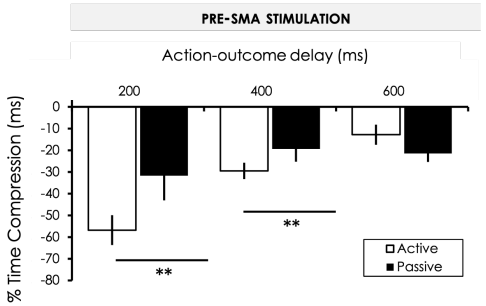
fMRI Results: At 200ms of action-outcome delay, the magnitude of the intentional binding effect was mirrored by meaningful brain activity in a broad network, including the bilateral insula, precuneus and cerebellum, the left pre-SMA, the left hippocampus, the right superior frontal gyrus, and the right inferior parietal lobule.



Study two, chapter three

Aim: Extending the investigation of the neural correlates of the sense of agency by measuring the effects of locally interfering with the brain activity of the identified agency network on the sense of agency experience.

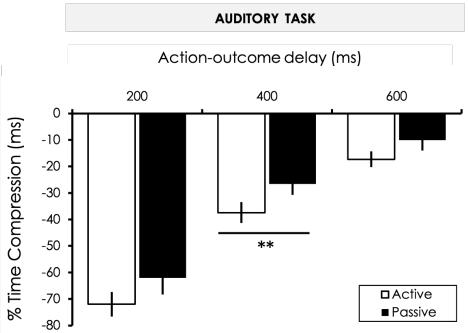
Results: When rTMS was applied over the pre-SMA before the action execution, participants showed an intentional binding effect even for longer delays, expanding the time-window for the intentional binding effect from 200ms of delay up to 400ms.
The stimulation of the same area after the motor execution did not produce any significant change with respect to the baseline. At the same time, modulating the parietal site with rTMS did not significantly affect the binding effect in any timing of stimulation.



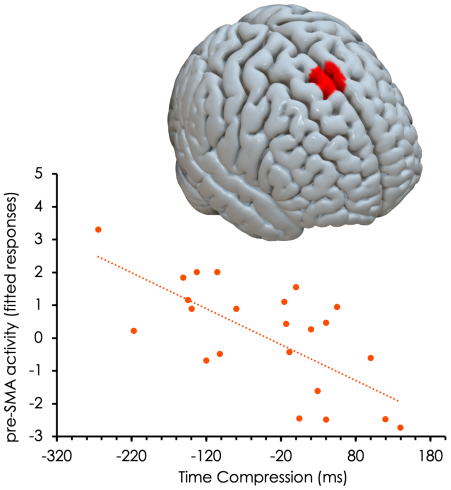
Study three, chapter four

Aim: Assessing the agency experience, and its neurofunctional mechanisms, for different action consequences compared to those tested in the previous fMRI study.

Behavioral Results: The results showed an intentional binding effect when the auditory outcome followed the voluntary action by 400ms.



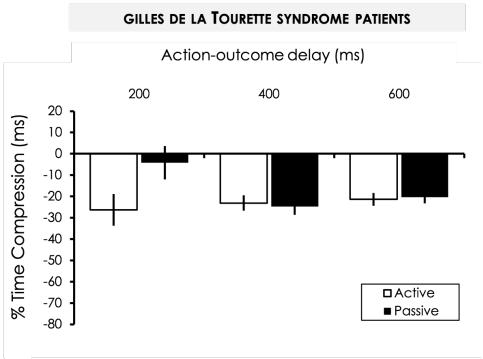
fMRI Results: At 400ms of action-outcome delay, the magnitude of the intentional binding effect was mirrored by meaningful brain activity in the pre-SMA.



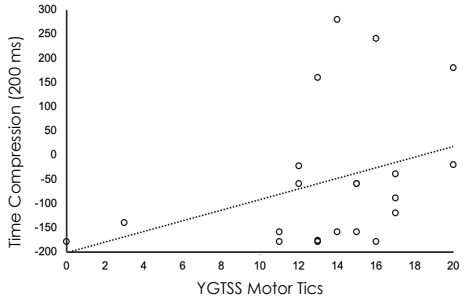
Study four, chapter five

Aim: Investigating the sense of agency, and its neurofunctional bases, in a clinical population affected by Gilles de la Tourette syndrome, a movement disorder characterized by unwanted movements called tics.

Behavioral Results: Gilles de la Tourette patients, as a group, did not show the expected intentional binding effect.



The greater the severity of motor tics, as measured by the YGTSS scale, the more reduced the time compression for intentional acts.



fMRI Results: At a neurofunctional level, GTS patients did not show any noticeable activity of the brain areas that showed a significant correlation with the magnitude of intentional binding phenomenon in healthy subjects.

Figure 1 | Synopsis of the main results of this thesis.

Sense of agency and pre-Supplementary Motor Cortex

The sense of agency is not a given, neither a transcendental feature of human nature. Instead, the brain appears to construct it actively. In this PhD thesis, I found that the sense of agency is the result of the activity of specific brain areas. Among them, the pre-SMA has proven to be the main character in the sense of agency storyline, showing not only a significant correlation with the intentional binding effect (study one, chapter two) but also a causal role in its generation (study two, chapter three). In addition, disorders of the sense of agency in Gilles de la Tourette syndrome have shown to be associated with a lack of association between the intentional binding effect and the pre-SMA activity (study four, chapter five).

There is independent evidence of a link between pre-SMA and the sense of agency. For example, EEG evidence showed that self-initiated movements following early readiness potentials - which has been related to the pre-SMA activity (Shibasaki and Hallett 2006) - result in a stronger binding effect compared to positive potentials (Jo et al. 2014). Non-invasive brain stimulation evidence suggested that transcranial direct current stimulation (tDCS) over the pre-SMA reduces the intentional binding effect towards auditory outcomes (Cavazzana et al. 2015). Also, a study with patients with corticobasal syndrome showed that functional connectivity patterns between the pre-SMA and the prefrontal cortex in resting conditions change according to the intentional binding effect (Wolpe et al. 2014). Taken together, all these results suggest a possible association between the sense of agency and the medial prefrontal cortex. However, this is the first time that the compelling link between the sense of agency and pre-SMA is demonstrated by a relevant set of evidence coming from different neuroscientific techniques, involving both healthy and pathological subjects, within a coherent experimental setting across studies.

The sense of agency as a phenomenon anchored to the functioning of the motor system

The link between the sense of agency and the pre-SMA is meaningful. Pre-SMA is a key structure for preparing and initiating voluntary actions, showing greater activity for self-initiated movements compared with externally triggered actions (Cunnington et al. 2003,

Zapparoli et al. 2018). Its electrical stimulation also causes a feeling of "urge" to move a specific body part in the absence of any detectable physical movement (Fried et al. 1991). Moreover, attending to the intention to move activates the pre-SMA (Lau et al. 2004). All these considerations then suggest that pre-SMA is associated with higher-level motor functions than the mere movement execution. The results presented in this thesis combined with previous evidence supporting the pre-SMA role in the intentional control of actions thus support the view that the brain mechanisms that give rise to the sense of agency are anchored to the functioning of the motor system (Frith et al. 2000, Wolpert et al. 1995, Wolpert and Ghahramani 2000), and, precisely, to the premotor brain activity specifically associated with *voluntary motor control*. These considerations allow several conclusions about the sense of agency.

First, they suggest that the sense of agency is tied to the source of the action. In other words, the conscious experience of action can be directly related to the underlying neural motor processes that cause the action itself. It follows that there is apparently no need for a superordinate system that generates awareness for the movement being executed. Instead, the motor system seems to generate its own awareness independently, as an emergent property of the system itself.

Second, this conscious experience of action seems to be constructed at the time of the action itself. More precisely, the sense of agency starts growing at the time of the action planning, when the premotor brain activity is setting the stage for the motor execution. At the same time, it is worth noting that the results in this thesis suggest that the sense of agency arises through a long-term process that accompanies the entire course of the action, starting at the time of the premotor brain activity of the pre-SMA, but not exhausting in it. Indeed, I have shown that the subjective experience of agency seems to be profoundly influenced by the action-outcome, at a time far away from the premotor brain activity that precedes the action itself (study three, chapter four).

In addition, the strong association between the sense of agency and premotor brain activity seems to suggest that the subjective experience of agency is tied to the specific motor act that follows a precise premotor activity. In this sense, the sense of agency refers to an experience that accompanies the performance of a specific actual movement than a general belief about the feasibility of unspecified action.

Furthermore, considering the sense of agency as an emergent property of the motor system ensures that the sense of agency can be studied scientifically using the methods of the

experimental investigation of the motor phenomena. It follows that the introspective methods for the study of the sense of agency should be abandoned in favor of objective and reproducible measures, a purpose pursued through all the experiments contained in this thesis.

However, it is worth noting that considering the sense of agency as an emergent property of the motor circuits that generate and control the action does not necessarily make sense of agency an immediate by-product of the motor system. Crucially, the link between the pre-SMA activity and the sense of agency resulted from a regression analysis with the putative marker of the sense of agency, i.e., the intentional binding effect. The greater the pre-SMA activation, the stronger the individually measured intentional binding effect (study one, chapter two). It follows that the pre-SMA activity does not reflect the pure effect of voluntary motor planning compared to the passive execution of the movement. Moreover, further evidence of the compelling link between the motor system and the sense of agency comes from the observation of clinical syndromes showing a disorder of the sense of agency. Gilles de la Tourette syndrome patients who did not report a significant intentional binding effect did not show any noticeable correlation between the pre-SMA activity and the magnitude of intentional binding phenomenon (study four, chapter five). However, it is worth noting that patients and healthy controls did not significantly differ for the brain activations related to the voluntary motor control in general, not directly associated with the sense of agency measure. Taken together, this evidence suggests that the neural mechanisms responsible for the sense of agency are closely related to the premotor brain activity that precedes the voluntary motor control, but, at the same time, a simple premotor mechanism cannot solely explain the pre-SMA activation related to the sense of agency. This leaves the specific contribution of the pre-SMA in the generation of the sense of agency unspecified.

The pre-SMA as a predictive area in the sense of agency generation

The specific role of the pre-SMA activity in the creation of the sense of agency is still unclear. One possibility is that the pre-SMA contributes to the self-agency experience using motor information to generate *predictions* of the sensory consequences of the action. The role of predictions in motor control is widely recognized (Frith et al. 2000, Wolpert et al. 1995, Wolpert and Ghahramani 2000, Adams et al. 2013, Friston et al. 2013). Predicting the sensory consequences of the incoming movement is essential to accomplish the current motor programs

and efficiently process the incoming sensory stimuli (Wolpert et al. 1995, Wolpert and Ghahramani 2000), and its role in attributing the external effects of self-generated movements to oneself is also widely accepted (Blakemore et al. 2002, Frith et al. 2000). One may then hypothesize that, due to its involvement in voluntary motor control (Zapparoli, Seghezzi and Paulesu 2017, Zapparoli et al. 2018, Lau et al. 2004), the pre-SMA might use the motor information to generate reliable predictions over the sensory consequences of the action. A predictive role is consistent, for example, with subdural recordings from the pre-SMA. Ikeda et al. (1999) have demonstrated the pre-SMA function in anticipating forthcoming stimuli, aside from motor preparation (Ikeda et al. 1999). A predictive role is also consistent with the results of the TMS study (study two, chapter three), showing that interfering with the activity of pre-SMA before the action execution significantly affects the behavioral manifestation of the sense of agency. In this study, I showed that when rTMS is applied over the pre-SMA in a premotor phase (*experiment one*, chapter three), the time window for the sense of agency experience is less precise. One possibility is that pre-SMA generated less accurate predictions about the outcome of the movement (for a deeper discussion on this hypothesis see chapter three) when stimulated with rTMS. As a consequence, this inefficient process may have caused an extension of the temporal window of tolerance for the expected outcome of actions, leading participants to treat as self-generated delayed consequences that are normally rejected as non-self-induced. The link between the pre-SMA and the creation of motor predictions thus seems convincing. However, further studies are needed to test the specific hypotheses that follow this speculation. For example, the origins of predictions remain to be explained. One possibility is that predictions result from the consolidation of the recurrent association between actions and outcomes. After the exposition of constant associations between certain acts and the following outcomes, the brain might learn to expect the outcomes given the action. Those predictions might be then updated by new incoming evidence when they fail to anticipate the status of the system. In other words, when predictions are no longer able to anticipate the incoming stimulation, they might change to reduce the discrepancy. How this prediction updating happens is still debated. The active inference theory (Adams et al. 2013, Brown et al. 2013, Friston et al. 2011, Friston et al. 2013) suggests that the influence of conflicting sensory evidence may determine an updating of the predictions based on their precision-weighting. Afferent signals with high precision may induce a more substantial updating of top-down predictions. Conversely, less precise sensory evidence may generate a mild update. For

example, a sensory input received on a foggy day may be less precise than compared to the same stimulus on a clear day. In the first case, we should rely more on our previous beliefs than new incoming sensory evidence to guide our behavior. In the second case, instead, we might rely more on the visual sensory stimuli than on previous expectations. In this case, new incoming highly precise evidence suggesting a change in our path would be more effective in updating predictions to accommodate our behavior to the new evidence. Although fascinating, much of this is hypothetical. Clearly, further research explicitly testing the predictions made by these speculations is required.

A construct validity of the implicit sense of agency

Crucially, it is worth noting that the results presented in this thesis and the ensuing considerations restrict themselves to a digression about an implicit sense of agency (i.e., the feeling of agency). This thesis did not address the explicit experience of agency that occurs when people explicitly think about their agentic role. As mentioned, it has been proposed that the sense of agency should be split into a "judgment of agency" and a "feeling of agency" (Synofzik et al. 2008a). The judgment of agency refers to the conceptual, interpretative judgment of being an agent. It arises when the agent makes explicit attribution of agency for an action or an event to the self or other. It requires higher-level cognitive processes, such as prior beliefs and conscious access to contextual information relating to the event. Instead, the feeling of agency represents the non-conceptual, low-level feeling of being the agent of an action. It represents the intangible sense of being in control of the action that flows in the background on the agent's stream of thoughts. It does not require conscious control, and it relies on low-level sensorimotor cues and contingencies (Synofzik et al. 2008b). The intentional binding effect measure of agency adopted in this thesis is linked to the lower-level implicit aspect of the sense of agency than the explicit judgment of being the agent of an action (Moore and Haggard 2010). Consequently, all the considerations proposed so far specifically addressed the implicit, elusive feeling of being in control with an action while they cannot be appliable to the explicit, conscious sense of agency.

It is indeed reasonable to expect different brain mechanisms for the feeling of agency and the judgment of agency. While the lower-level feeling of agency is linked to the sensorimotor system, the judgment of agency is probably associated with higher-level associative cortices.

For example, in a recent study, Renes et al. (2016) showed that self-agency inferences were associated with activation in the medial prefrontal cortex and the bilateral (medial) superior frontal gyrus (Renes et al. 2015). These medial frontal regions have been found to be involved with self-referential processing (van Buuren et al. 2010) and wider inferential processing, such as trait inferences (Ma et al. 2011) and understanding others' actions and goals (Van Overwalle and Baetens 2009). Such a brain network thus offers access to higher-level cognitive processes needed to infer whether the agent the cause of some somatosensory exteroceptive input, as opposed to another agent, and formulate explicit judgments of agency.

Certainly, it would be then interesting to explore how the implicit and explicit sense of agency and their respective neural networks influence each other and interact to generate a coherent sense of self in the agent.

Implications for understanding and treating disorders of the sense of agency

The results in this thesis showed that the feeling of agency arises as an emergent property of the motor system. The sense of agency maps into the underlying neural motor processes that cause the action itself, particularly within the premotor brain circuits that program and control the execution of the intentional actions. This evidence has several implications for understanding and treating disorders of the sense of agency.

A first important consideration suggests that every syndrome affecting the motor system might somehow affect the sense of agency. Disturbances of the sense of agency have indeed been shown in several movement disorders, i.e., clinical syndromes that cause either an excess of involuntary movement or a paucity of voluntary movements, unrelated to the patient's intention. For example, Saito et al. (2017) showed that Parkinson's disease patients are inclined to attribute their action feedback to themselves less often than healthy subjects. Moore et al. (2010b) reported that Parkinson's patients on medication show a significant increase in action-effect binding relative to their performance off medication and controls. Moreover, Wolpe et al. (2018) showed that the degree of sensory attenuation is negatively related to Parkinson's disease motor severity but positively related to individual dopamine dose, measured by levodopa dose equivalent. Wolpe et al. (Wolpe et al. 2014) showed an abnormal binding in corticobasal syndrome patients relative to control subjects, with an increased temporal

attraction of the action toward the subsequent tone in the more-affected hand. The increase correlated with the severity of the alien limb and apraxia in that hand. Moreover, differences in binding were related to structural changes in pre-SMA grey matter and functional connectivity at rest between the pre-supplementary motor area and prefrontal cortex. Growing evidence has shown a major impairment in the sense of agency experience also in people suffering from Psychogenic movement disorders. This impairment is evident in patients' subjective reports (Nahab et al. 2017), as well as in indirect indexes of agency, like intentional binding (Kranick et al. 2013) and sensory attenuation (Pareés et al. 2014) and seems to be specifically linked to the activity of the pre-SMA (Nahab et al. 2017). Gilles de la Tourette syndrome has become a matter of subject for the agency investigation only recently. Delorme and colleagues (2016) first tested patients' ability to recognize incongruences between their actions and feedback and to make appropriate judgments of agency. They showed that Gilles de la Tourette syndrome patients do not realize that they were not fully responsible for the outcome and, instead, they inflate their judgment of agency (Delorme, Salvador, et al., 2016). Added to this is the evidence that Gilles de la Tourette syndrome patients do not report an intentional binding effect for voluntary actions, and neither do they show the typical premotor pattern of activation associated with the normal sense of agency experience (study four, chapter five). Aberrant experiences of agency can also be seen in acquired movement disorders, like anosognosia for hemiplegia. Those patients typically suffer from right-brain damage that causes a paresis of the left side of the body, but they persistently deny their motor impairment, and when asked to move their paralyzed limb, they claim to have performed the required movement (Fotopoulou 2012, Pia et al. 2004). It follows that those patients can experience a sense of agency for movements that they cannot make, and for which there is sensory evidence to confirm the impossibility of movement (Moore 2016).

From this brief and incomplete analysis of the clinical research on the sense of agency, it should be evident that abnormal experiences of agency are dramatically common in a range of different movement disorders. At the same time, the main role of the pre-SMA in those disturbances looks undeniable. On the one hand, this evidence confirms the sense of agency as a phenomenon anchored to the functioning of the motor system. On the other hand, it leaves the question for future research to determine whether different aberrant experiences of agency seen in multiple disorders may share the same dysfunctional mechanisms.

A second important consideration regards how to use this knowledge about the agency subjective experience and its neural correlates to develop interventions aimed at remedying disorders of the sense of agency.

The results in this thesis showed that the conscious experience of action relies on appropriate temporal and predictive relations between preparation, movement, and effect. One possibility for treatment may thus aim at restoring this putative link between accurate predictions and action-outcome. Previous studies have already shown that this link is subject to possible change. For example, Hearing et al. (2015) showed that when participants were exposed to immediate action-effects, they felt less in control, the longer the delay between the action and the effect. In contrast, participants who were exposed to delayed effects showed the reversed result pattern and sensed less agency, the shorter the delay between action and effect (Haering and Kiesel 2015). Similarly, Kilteni et al. (2019) found that participants experienced less sensory attenuation for non-delayed self-generated touch after exposure to systematic delays. Conversely, they perceived as less intense - and thus attenuated - the delayed self-generated stimuli to which they were exposed (Kilteni et al. 2019). These results suggest that the sense of agency includes an important element of perceptual learning of the association between actions and effects. Precisely, people seem to learn to predict the effects of their own actions from previous associative learning. It follows that learning new action-effect associations seems possible. How this happens in the brain remains to be explored. As mentioned before, one possibility is that the brain acts by updating the predictions to null discrepancies between predictions and sensory evidence resulting in a prediction error. However, it remains to be discovered if it is possible to update predictions based on action-outcome associations well-established in our memory. While it can be relatively easy to modify action-outcome associations established in a laboratory setting upon meaningless stimuli, it may be more difficult to intervene on real-file action-outcome associations. For example, the association between pressing an electric light-switch and the turning on of a lamp may be hard to tune to new temporal intervals incompatible with the everyday experience. Moreover, it is unclear how long the effects of habituation training as those proposed by Hearing (2015) and Kilteni (2019) may last in time. Future research should test and develop training able to induce permanent changes in patients' life.

Alternatively, another possibility for treatment could rely on interventions that act upon the reconstructive thinking suggested by "apparent mental causation" theory (Wegner 2003).

Although I did not find explicit evidence in favor of any reconstructive mechanism in this thesis (see the next paragraph), the role of "postdiction" in the sense of agency has been confirmed by studies in which the probability of the outcome was experimentally manipulated so as to make the contribution of motor predictions negligible (Moore and Haggard 2008). Training patients to consciously reconstruct their own agency could provide them with an alternative high-level strategy to infer a sense of agency when lower-level predictive mechanisms are irremediably damaged.

A strategy based on habituation training might be optimal for those suffering from metacognitive problems, like schizophrenic patients (Kircher et al. 2007). In this case, inferential thinking is probably too damaged to be restored. A metacognitive strategy, instead, could be adopted in case of the failure of strategies based on implicit learning. In this case, training the inferential thinking may help patients developing different higher-level strategies to infer an appropriate sense of agency for actions.

Do the present findings permit to identify a best fitting theory of the sense of agency?

The role of predictions on action awareness is widely recognized by serval theories of motor control. As mentioned in the introductive chapter, the predictive component of the sense of agency has drawn on concepts from optimal motor control theory (Franklin and Wolpert 2011, Wolpert and Ghahramani 2000) within the comparator model (Blakemore et al. 2002, Frith et al. 2000). The comparator model suggests that the sense of agency arises from a comparison between the predicted and actual sensory feedback of the action. If the predicted outcome matches the actual sensory effect, the outcome is perceived as self-generated. When there is a mismatch between the predicted and the actual action-outcome, this is perceived as externally generated, independent of one's own volition (Haggard 2017). There is little doubt in this thesis about the importance of premotor action planning signals, particularly sensorimotor predictions, for the sense of agency. However, the reader may be surprised by the lack of evidence about a possible comparator mechanism responsible for the comparison between the predicted and actual sensory feedback of the action. Admittedly, the hypothesis of a predictor and a comparator guided the selection of the target areas for stimulation in the rTMS study presented in this thesis (chapter three) among the broad brain network associated with the sense

of agency resulting from the fMRI study (chapter two). Precisely, it is well known that the pre-SMA is primarily concerned with the voluntary movement generation (Zapparoli et al. 2018, Lau et al. 2004), while the parietal lobule is involved in the high-order processing of sensory and multisensory inputs and with the representation of the external space and the body (Berlucchi and Vallar 2018). Consequently, I reasoned that both target regions might contribute to the sense of agency, but they may be distinguishable in terms of both their function and time of contribution. Specifically, while the pre-SMA may contribute to the generation of predictions before the action execution in a pre-motoric phase, I expected the parietal lobule to play a role in a later phase when the consequences of the action are available to be compared with the predictions for the attribution of the sense of agency. While the results provided support for the first component, showing the causal role of the pre-SMA in a premotor, "predictive", phase of the sense of agency generation, the parietal stimulation did not affect the sense of agency when applied in a putative "comparative" phase, at the appearance of the action effects. Obviously, care is needed in interpreting the parietal results. Indeed, the lack of evidence suggesting a role for parietal cortices in the putative comparative phase of the sense of agency generation is not sufficient to exclude the existence of a comparator in toto. The absence of any effect of the stimulation may be due to certain uncontrolled experiment features. For example, in principle, it would have been interesting to investigate the rTMS effect also on the cerebellar activation foci resulting from the fMRI experiment. However, these were too deep to realistically hope to achieve a selective modulation. Another possibility is that there is no need for a supra comparator area, as suggested by the comparator model. Instead, the prediction errors may arise in the low-level sensory cortices specific for the incoming stimulus[8]. This hypothesis is in line with the recent concepts from the active inference theory (Adams et al. 2013, Brown et al. 2013, Friston et al. 2011, Friston et al. 2013). According to the active inference account, the sense of agency arises from the ability of higher levels of the cortical hierarchy (e.g., pre-SMA) to predict sensory data from lower levels through movement. Critically, the sense of agency depends on a balance in the precision of prediction errors within the cortical hierarchy for the action, and the ability of the hierarchy to converge on the agent as the most likely cause of a sensation (Wolpe and Rowe 2014). It is worth noting from the graphical representation below (**Figure 2**) that basing on the active inference account, there are several comparators for specific

[1] It is worth noting that the occipital control site used in the rTMS experiment was too lateralized on the left respect the expected occipital activation for a stimulus presented at the centre of the screen.

predictions and sensory evidence, while there is no need for a superordinate comparator. Instead, the comparison should be processed into the low-level (sensory) nodes in a distributed circuit underlying sensorimotor integration.

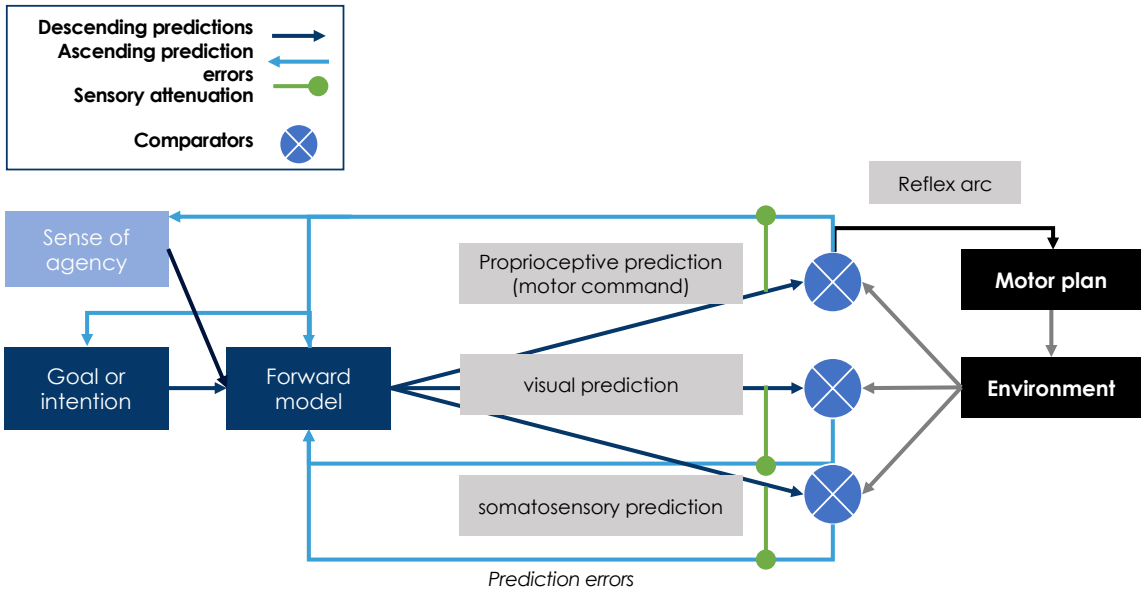


Figure 2 | Graphical representation of the active inference model for the sense of agency, adapted from Friston (2020, personal communication).

Although the active inference principles have not yet been experimentally applied to the study of agency, this theory is a promising candidate to accommodate within the same framework the comparator model (Frith et al. 2000, Wolpert and Ghahramani 2000) and the newest experimental evidence. For example, a formal model of agency based on active inference includes feedback connections from the environment to the forward model that allow the updating of descending predictions. The theory thus offers a helpful and novel research opportunity for the investigation of the sense of agency, focusing on testing parameters of brain connectivity within hierarchical networks (Wolpe and Rowe 2014).

However, it is worth noticing that the formal model of agency proposed by active inference restricts itself to a construct validation of an implicit sense of agency (i.e., the feeling of agency). This model can't explain the explicit sense of agency, in which subjects have to report their subjective experience of agency. It has been discussed that an explicit level of agency requires higher-level cognitive processes, such as prior beliefs and conscious access to contextual information relating to the event that intervene both prior and after the action

execution, through a process of sense-making (Synofzik et al. 2008a, Synofzik et al. 2008b). The importance of such postdictive contribution of the high-levels beliefs in the sense of agency generation has been first emphasized in the apparent mental causation theory (Wegner 2003). More recently, other theories of agency have argued for integration between predictive sensorimotor signals and high-level postdictive cues for generating a sense of agency (Moore et al. 2009, Moore and Fletcher 2012, Synofzik et al. 2008a, Synofzik et al. 2008b). Importantly, the explicit sense of agency has not been explored in this thesis. However, future works that will accept the active inference principles for the studying of agency must integrate an active inference model of the explicit sense of agency. This would require the evaluation of evidence for two hypotheses "did I do that, or did you do that?". In this view, the model should include high-level representations that would be necessary to infer whether I am the cause of some somatosensory exteroceptive input, as opposed to another agent. Those inferences about agency would depend upon belief updating from all modalities – and represent a high-level inference about the context in which an action was experienced. See below a graphical representation of the model (**Figure 3**).

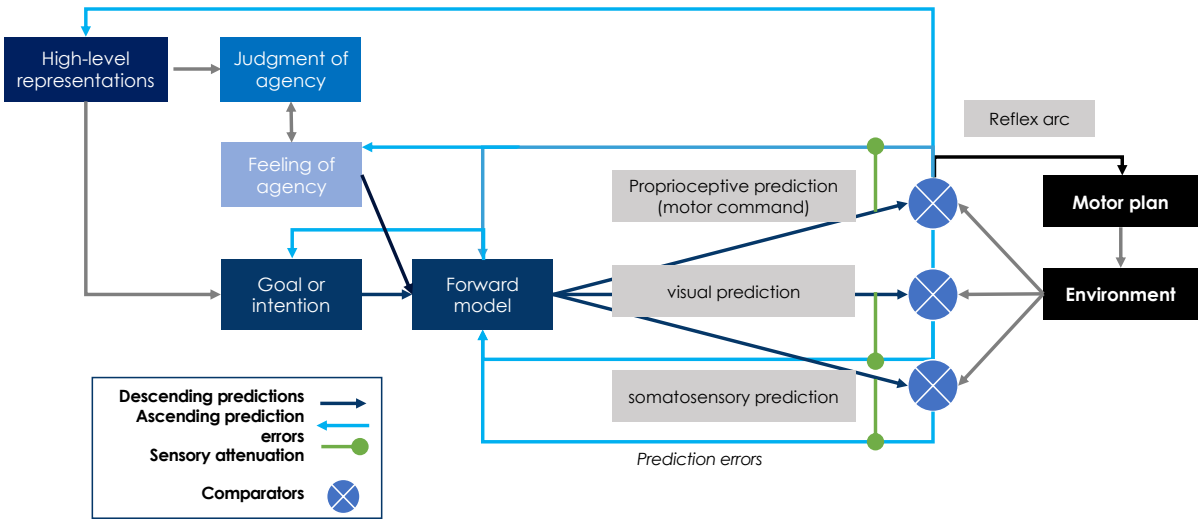


Figure 3 | Graphical representation of an integrative model for the sense of agency based on the active inference, adapted from Friston (2020, personal communication).

In summary, although identifying the best fitting theory of the sense of agency was not part of the main purposes of this thesis, the present data tip in favor of an integrative model of the sense of agency that includes a superordinate mechanism of attributing agency from higher-level beliefs and priors, besides the seminal forward mechanism for the feeling of agency, within the newest framework of the active inference theory.

Active inference provides an appealing attempt to develop a mechanistic account for the sense of agency, able to unify different theories within a unique framework. From this model, a number of specific testable hypotheses emerge regarding the functional role of the primary sensorimotor cortices, the sensory attenuation, and the neurophysiological correlate of changes in sensory precision. However, while this theory is grounded in computational and theoretical work, it still lacks full validation through converging neurofunctional empirical evidence.

Conclusions and future directions

In this thesis, I explored the subjective experience of agency and its neural correlates. I showed that the sense of agency is the result of the activity of specific brain areas, including, in particular, the medial prefrontal cortex. The premotor nature of the sense of agency brain network allowed me to draw some considerations about how the sense of agency is constructed into the brain and how it can be rehabilitated when dramatically damaged. Moreover, the results in this thesis allowed me to hypothesize a predictive role for the pre-SMA in the sense of agency generation. Those results - although far from being conclusive – can be inscribed within the broad theoretical framework of the active inference. This perspective offers a different research framework for future sense of agency investigations, focusing on testing parameters of brain connectivity between regions (for example, using Dynamic Causal Modelling analysis), rather than looking for discrete and independent contributes of different regions.

References

Adams, R. A., S. Shipp & K. J. Friston (2013) Predictions not commands: active inference in the motor system. *Brain Struct Funct,* 218**,** 611-43.

Adler, L. A., T. Spencer, S. V. Faraone, R. C. Kessler, M. J. Howes, J. Biederman & K. Secnik (2006) Validity of pilot Adult ADHD Self- Report Scale (ASRS) to Rate Adult ADHD symptoms. *Ann Clin Psychiatry,* 18**,** 145-8.

Ashburner, J. & K. J. Friston (1999) Nonlinear spatial normalization using basis functions. *Hum Brain Mapp,* 7**,** 254-66.

Baess, P., J. Horváth, T. Jacobsen & E. Schröger (2011) Selective suppression of self-initiated sounds in an auditory stream: An ERP study. *Psychophysiology,* 48**,** 1276-83.

Balslev, D., F. A. Nielsen, T. E. Lund, I. Law & O. B. Paulson (2006) Similar brain networks for detecting visuo-motor and visuo-proprioceptive synchrony. *Neuroimage,* 31**,** 308-12.

Bandura, A. 1982. Self-efficacy mechanism in human agency., 122–147. Am. Psychol.

Bays, P. M., J. R. Flanagan & D. M. Wolpert (2006) Attenuation of self-generated tactile sensations is predictive, not postdictive. *PLoS Biol,* 4**,** e28.

Beck, A. T., et al. (1961) "Beck depression inventory (BDI)." *Arch Gen Psychiatry 4.6* 561-571.

Berlucchi, G. & G. Vallar (2018) The history of the neurophysiology and neurology of the parietal lobe. *Handb Clin Neurol,* 151**,** 3-30.

Berti, A., G. Bottini, M. Gandola, L. Pia, N. Smania, A. Stracciari, I. Castiglioni, G. Vallar & E. Paulesu (2005) Shared cortical anatomy for motor awareness and motor control. *Science,* 309**,** 488-91.

Blakemore, S. J., C. D. Frith & D. M. Wolpert (2001) The cerebellum is involved in predicting the sensory consequences of action. *Neuroreport,* 12**,** 1879-84.

Blakemore, S. J., D. Wolpert & C. Frith (2000) Why can't you tickle yourself? *Neuroreport,* 11**,** R11-6.

Blakemore, S. J., D. M. Wolpert & C. D. Frith (1998) Central cancellation of self-produced tickle sensation. *Nature neuroscience*.

--- (2002) Abnormalities in the awareness of action. *Trends Cogn Sci,* 6**,** 237-242.

Bohlhalter, S., A. Goldfine, S. Matteson, G. Garraux, T. Hanakawa, K. Kansaku, R. Wurzman & M. Hallett (2006) Neural correlates of tic generation in Tourette syndrome: an event-related functional MRI study. *Brain,* 129**,** 2029-37.

Brown, H., R. A. Adams, I. Parees, M. Edwards & K. Friston (2013) Active inference, sensory attenuation and illusions. *Cogn Process,* 14**,** 411-27.

Buehner, M. J. & G. R. Humphreys (2009) Causal binding of actions to their effects. *Psychol Sci,* 20**,** 1221-8.

Burd, L., P. J. Kerbeshian, A. Barth, M. G. Klug, P. K. Avery & B. Benz (2001) Long-term follow-up of an epidemiologically defined cohort of patients with Tourette syndrome. *J Child Neurol,* 16**,** 431-7.

Cath, D. C., T. Hedderly, A. G. Ludolph, J. S. Stern, T. Murphy, A. Hartmann, V. Czernecki, M. M. Robertson, D. Martino, A. Munchau, R. Rizzo & E. G. Group (2011) European clinical guidelines for Tourette syndrome and other tic disorders. Part I: assessment. *Eur Child Adolesc Psychiatry,* 20**,** 155-71.

Cauda, F., F. D'Agata, K. Sacco, S. Duca, G. Geminiani & A. Vercelli (2011) Functional connectivity of the insula in the resting brain. *Neuroimage,* 55**,** 8-23.

Cavanna, A. E. & A. Nani (2013) Tourette syndrome and consciousness of action. *Tremor Other Hyperkinet Mov (N Y),* 3.

Cavazzana, A., B. Penolazzi, C. Begliomini & P. S. Bisiacchi (2015) Neural underpinnings of the 'agent brain': new evidence from transcranial direct current stimulation. *Eur J Neurosci,* 42**,** 1889-94.

Chambon, V., J. W. Moore & P. Haggard (2015) TMS stimulation over the inferior parietal cortex disrupts prospective sense of agency. *Brain Struct Funct,* 220**,** 3627-39.
Chambon, V., D. Wenke, S. M. Fleming, W. Prinz & P. Haggard (2013) An online neural substrate for sense of agency. *Cereb Cortex,* 23**,** 1031-7.
Cohen, S. C., J. F. Leckman & M. H. Bloch (2013) Clinical assessment of Tourette syndrome and tic disorders. *Neurosci Biobehav Rev,* 37**,** 997-1007.
Colle, L., D. Hilviu, R. Rossi, F. Garbarini & C. Fossataro (2020) Self-Harming and Sense of Agency in Patients With Borderline Personality Disorder. *Front Psychiatry,* 11**,** 449.
Cullen, A. C. & H. C. Frey. 1999. *Probabilistic Techniques in Exposure Assessment. A Handbook for Dealing with Variability and Uncertainty in Models and Inputs.* . New York and London: Plenum Press.
Cunnington, R., C. Windischberger, L. Deecke & E. Moser (2003) The preparation and readiness for voluntary movement: a high-field event-related fMRI study of the Bereitschafts-BOLD response. *Neuroimage,* 20**,** 404-12.
Daprati, E., N. Franck, N. Georgieff, J. Proust, E. Pacherie, J. Dalery & M. Jeannerod (1997) Looking for the agent: an investigation into consciousness of action and self-consciousness in schizophrenic patients. *Cognition,* 65**,** 71-86.
David, N., M. X. Cohen, A. Newen, B. H. Bewernick, N. J. Shah, G. R. Fink & K. Vogeley (2007) The extrastriate cortex distinguishes between the consequences of one's own and others' behavior. *Neuroimage,* 36**,** 1004-14.
de Bézenac, C. E., V. Sluming, A. Gouws & R. Corcoran (2016) Neural response to modulating the probability that actions of self or other result in auditory tones: A parametric fMRI study into causal ambiguity. *Biol Psychol,* 119**,** 64-78.
Delorme, C., E. Roze, D. Grabli, J. M. Mayer, B. Degos, M. Vidailhet & Y. Worbe (2016a) Explicit Agency in Patients with Cervical Dystonia: Altered Recognition of Temporal Discrepancies between Motor Actions and Their Feedback. *PLoS One,* 11**,** e0162191.
Delorme, C., A. Salvador, V. Voon, E. Roze, M. Vidailhet, A. Hartmann & Y. Worbe (2016b) Illusion of agency in patients with Gilles de la Tourette Syndrome. *Cortex,* 77**,** 132-40.
Desantis, A., C. Roussel & F. Waszak (2011) On the influence of causal beliefs on the feeling of agency. *Conscious Cogn,* 20**,** 1211-20.
Dubois, B., A. Slachevsky, I. Litvan & B. Pillon (2000) The FAB: a Frontal Assessment Battery at bedside. *Neurology,* 55**,** 1621-6.
Eickhoff, S. B., A. R. Laird, C. Grefkes, L. E. Wang, K. Zilles & P. T. Fox (2009) Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: a random-effects approach based on empirical estimates of spatial uncertainty. *Hum Brain Mapp,* 30**,** 2907-26.
Engbert, K. & A. Wohlschläger (2007) Intentions and expectations in temporal binding. *Conscious Cogn,* 16**,** 255-64.
Engbert, K., A. Wohlschläger & P. Haggard (2008) Who is causing what? The sense of agency is relational and efferent-triggered. *Cognition,* 107**,** 693-704.
Farrer, C., M. Bouchereau, M. Jeannerod & N. Franck (2008a) Effect of distorted visual feedback on the sense of agency. *Behav Neurol,* 19**,** 53-7.
Farrer, C., N. Franck, N. Georgieff, C. D. Frith, J. Decety & M. Jeannerod (2003) Modulating the experience of agency: a positron emission tomography study. *Neuroimage,* 18**,** 324-33.
Farrer, C., S. H. Frey, J. D. Van Horn, E. Tunik, D. Turk, S. Inati & S. T. Grafton (2008b) The angular gyrus computes action awareness representations. *Cereb Cortex,* 18**,** 254-61.
Farrer, C. & C. D. Frith (2002) Experiencing oneself vs another person as being the cause of an action: the neural correlates of the experience of agency. *Neuroimage,* 15**,** 596-603.
Flandin, G. & K. J. Friston (2017) Analysis of family-wise error rates in statistical parametric mapping using random field theory. *Hum Brain Mapp*.
Folstein, M. F., S. E. Folstein & P. R. McHugh (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res,* 12**,** 189-98.

Fossati, A., A. Di Ceglie, E. Acquarini & E. S. Barratt (2001) Psychometric properties of an Italian version of the Barratt Impulsiveness Scale-11 (BIS-11) in nonclinical subjects. *J Clin Psychol,* 57**,** 815-28.
Fotopoulou, A. K. (2012) Illusions and delusions in anosognosia for hemiplegia: from motor predictions to prior beliefs. *Brain,* 135**,** 1344-6.
Franklin, D. W. & D. M. Wolpert (2011) Computational mechanisms of sensorimotor control. *Neuron,* 72**,** 425-42.
Fried, I., A. Katz, G. McCarthy, K. J. Sass, P. Williamson, S. S. Spencer & D. D. Spencer (1991) Functional organization of human supplementary motor cortex studied by electrical stimulation. *J Neurosci,* 11**,** 3656-66.
Friston, K. (2010) The free-energy principle: a unified brain theory? *Nat Rev Neurosci,* 11**,** 127-38.
Friston, K., J. Ashburner, C. Frith, J. Polline & H. J. (1995) Spatial registration and normalization of images. *Human Brain Mapping,* 2**,** 165-89.
Friston, K., J. Mattout & J. Kilner (2011) Action understanding and active inference. *Biol Cybern,* 104**,** 137-60.
Friston, K., P. Schwartenbeck, T. Fitzgerald, M. Moutoussis, T. Behrens & R. J. Dolan (2013) The anatomy of choice: active inference and agency. *Front Hum Neurosci,* 7**,** 598.
Friston, K. J., A. Holmes, J. B. Poline, C. J. Price & C. D. Frith (1996) Detecting activations in PET and fMRI: levels of inference and power. *Neuroimage,* 4**,** 223-35.
Frith, C. (2012) Explaining delusions of control: the comparator model 20 years on. *Conscious Cogn,* 21**,** 52-4.
Frith, C. D. (2014) Action, agency and responsibility. *Neuropsychologia,* 55**,** 137-42.
Frith, C. D., S. J. Blakemore & D. M. Wolpert (2000) Abnormalities in the awareness and control of action. *Philos Trans R Soc Lond B Biol Sci,* 355**,** 1771-88.
Fukushima, H., Y. Goto, T. Maeda, M. Kato & S. Umeda (2013) Neural substrates for judgment of self-agency in ambiguous situations. *PLoS One,* 8**,** e72267.
Ganos, C., L. Asmuss, J. Bongert, V. Brandt, A. Münchau & P. Haggard (2015) Volitional action as perceptual detection: predictors of conscious intention in adolescents with tic disorders. *Cortex,* 64**,** 47-54.
Ganos, C., V. Roessner & A. Münchau (2013) The functional anatomy of Gilles de la Tourette syndrome. *Neurosci Biobehav Rev,* 37**,** 1050-62.
Gentsch, A., S. Schütz-Bosbach, T. Endrass & N. Kathmann (2012) Dysfunctional forward model mechanisms and aberrant sense of agency in obsessive-compulsive disorder. *Biol Psychiatry,* 71**,** 652-9.
Goodman, W. K., L. H. Price, S. A. Rasmussen, C. Mazure, R. L. Fleischmann, C. L. Hill, G. R. Heninger & D. S. Charney (1989) The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. *Arch Gen Psychiatry,* 46**,** 1006-11.
Haering, C. & A. Kiesel (2015) Was it me when it happened too early? Experience of delayed effects shapes sense of agency. *Cognition,* 136**,** 38-42.
Haggard, P. (2005) Conscious intention and motor cognition. *Trends Cogn Sci,* 9**,** 290-5.
--- (2017) Sense of agency in the human brain. *Nat Rev Neurosci,* 18**,** 196-207.
Haggard, P., S. Clark & J. Kalogeras (2002) Voluntary action and conscious awareness. *Nat Neurosci,* 5**,** 382-5.
Haggard, P. & B. Eitam. 2015. *The sense of agency*. Social Cognition and Social Ne.
Haggard, P., F. Martin, M. Taylor-Clarke, M. Jeannerod & N. Franck (2003) Awareness of action in schizophrenia. *Neuroreport,* 14**,** 1081-5.
He, S. Q., R. P. Dum & P. L. Strick (1995) Topographic organization of corticospinal projections from the frontal lobe: motor areas on the medial surface of the hemisphere. *J Neurosci,* 15**,** 3284-306.
Holmes, A. & K. Friston (1998) Generalisability, random effects\ & population inference. *Neuroimage,* 7.
Hughes, G. (2018) The role of the temporoparietal junction in implicit and explicit sense of agency. *Neuropsychologia,* 113**,** 1-5.

Ikeda, A., S. Yazawa, T. Kunieda, S. Ohara, K. Terada, N. Mikuni, T. Nagamine, W. Taki, J. Kimura & H. Shibasaki (1999) Cognitive motor control in human pre-supplementary motor area studied by subdural recording of discrimination/selection-related potentials. *Brain,* 122 (Pt 5)**,** 915-31.

Jo, H. G., M. Wittmann, T. Hinterberger & S. Schmidt (2014) The readiness potential reflects intentional binding. *Front Hum Neurosci,* 8**,** 421.

Khalighinejad, N. & P. Haggard (2015) Modulating human sense of agency with non-invasive brain stimulation. *Cortex,* 69**,** 93-103.

Kilteni, K., C. Houborg & H. H. Ehrsson (2019) Rapid learning and unlearning of predicted sensory delays in self-generated touch. *Elife,* 8.

Kim, J. H., J. M. Lee, H. J. Jo, S. H. Kim, J. H. Lee, S. T. Kim, S. W. Seo, R. W. Cox, D. L. Na, S. I. Kim & Z. S. Saad (2010) Defining functional SMA and pre-SMA subregions in human MFC using resting state fMRI: functional connectivity-based parcellation method. *Neuroimage,* 49**,** 2375-86.

Kim, S., G. M. Jackson, K. Dyke & S. R. Jackson (2019) Impaired forward model updating in young adults with Tourette syndrome. *Brain,* 142**,** 209-219.

Kincade, J. M., R. A. Abrams, S. V. Astafiev, G. L. Shulman & M. Corbetta (2005) An event-related functional magnetic resonance imaging study of voluntary and stimulus-driven orienting of attention. *J Neurosci,* 25**,** 4593-604.

Kircher, T. T., K. Koch, F. Stottmeister & V. Durst (2007) Metacognition and reflexivity in patients with schizophrenia. *Psychopathology,* 40**,** 254-60.

Kontaris, I., A. J. Wiggett & P. E. Downing (2009) Dissociation of extrastriate body and biological-motion selective areas by manipulation of visual-motor congruency. *Neuropsychologia,* 47**,** 3118-24.

Kranick, S. M., J. W. Moore, N. Yusuf, V. T. Martinez, K. LaFaver, M. J. Edwards, A. R. Mehta, P. Collins, N. A. Harrison, P. Haggard, M. Hallett & V. Voon (2013) Action-effect binding is decreased in motor conversion disorder: implications for sense of agency. *Mov Disord,* 28**,** 1110-6.

Kurth, F., S. B. Eickhoff, A. Schleicher, L. Hoemke, K. Zilles & K. Amunts (2010a) Cytoarchitecture and probabilistic maps of the human posterior insular cortex. *Cereb Cortex,* 20**,** 1448-61.

Kurth, F., K. Zilles, P. T. Fox, A. R. Laird & S. B. Eickhoff (2010b) A link between the systems: functional differentiation and integration within the human insula revealed by meta-analysis. *Brain Struct Funct,* 214**,** 519-34.

Kühn, S., M. Brass & P. Haggard (2013) Feeling in control: Neural correlates of experience of agency. *Cortex,* 49**,** 1935-42.

Kühn, S., I. Nenchev, P. Haggard, M. Brass, J. Gallinat & M. Voss (2011) Whodunnit? Electrophysiological correlates of agency judgements. *PLoS One,* 6**,** e28657.

Lau, H. C., R. D. Rogers, P. Haggard & R. E. Passingham (2004) Attention to intention. *Science,* 303**,** 1208-10.

Leckman, J. F., M. H. Bloch, M. E. Smith, D. Larabi & M. Hampson (2010) Neurobiological substrates of Tourette's disorder. *J Child Adolesc Psychopharmacol,* 20**,** 237-47.

Leckman, J. F., M. A. Riddle, M. T. Hardin, S. I. Ort, K. L. Swartz, J. Stevenson & D. J. Cohen (1989) The Yale Global Tic Severity Scale: initial testing of a clinician-rated scale of tic severity. *J Am Acad Child Adolesc Psychiatry,* 28**,** 566-73.

Leube, D. T., G. Knoblich, M. Erb, W. Grodd, M. Bartels & T. T. Kircher (2003a) The neural correlates of perceiving one's own movements. *Neuroimage,* 20**,** 2084-90.

Leube, D. T., G. Knoblich, M. Erb & T. T. Kircher (2003b) Observing one's hand become anarchic: an fMRI study of action identification. *Conscious Cogn,* 12**,** 597-608.

Libet, B., C. A. Gleason, E. W. Wright & D. K. Pearl (1983) Time of conscious intention to act in relation to onset of cerebral activity (readiness-potential). The unconscious initiation of a freely voluntary act. *Brain,* 106 (Pt 3)**,** 623-42.

Ma, N., M. Vandekerckhove, F. Van Overwalle, R. Seurinck & W. Fias (2011) Spontaneous and intentional trait inferences recruit a common mentalizing network to a different degree: spontaneous inferences activate only its core areas. *Soc Neurosci,* 6**,** 123-38.
MacDonald, P. A. & T. Paus (2003) The role of parietal cortex in awareness of self-generated movements: a transcranial magnetic stimulation study. *Cereb Cortex,* 13**,** 962-7.
Mahayana, I. T., L. Tcheang, C. Y. Chen, C. H. Juan & N. G. Muggleton (2014) The precuneus and visuospatial attention in near and far space: a transcranial magnetic stimulation study. *Brain Stimul,* 7**,** 673-9.
Marotta, A., F. Bombieri, M. Zampini, F. Schena, C. Dallocchio, M. Fiorio & M. Tinazzi (2017) The Moving Rubber Hand Illusion Reveals that Explicit Sense of Agency for Tapping Movements Is Preserved in Functional Movement Disorders. *Front Hum Neurosci,* 11**,** 291.
Martikainen, M. H., K. Kaneko & R. Hari (2005) Suppressed responses to self-triggered sounds in the human auditory cortex. *Cereb Cortex,* 15**,** 299-302.
Martino, D., C. Ganos & Y. Worbe (2018) Neuroimaging Applications in Tourette's Syndrome. *Int Rev Neurobiol,* 143**,** 65-108.
Matsuzawa, M., K. Matsuo, T. Sugio, C. Kato & T. Nakai (2005) Temporal relationship between action and visual outcome modulates brain activation: an fMRI study. *Magn Reson Med Sci,* 4**,** 115-21.
Moore, J. & P. Haggard (2008) Awareness of action: Inference and prediction. *Conscious Cogn,* 17**,** 136-44.
Moore, J. W. (2016) What Is the Sense of Agency and Why Does it Matter? *Front Psychol,* 7**,** 1272.
Moore, J. W. & P. C. Fletcher (2012) Sense of agency in health and disease: a review of cue integration approaches. *Conscious Cogn,* 21**,** 59-68.
Moore, J. W. & P. Haggard (2010) Intentional binding and higher order agency experience. *Conscious Cogn,* 19**,** 490-1.
Moore, J. W., D. Middleton, P. Haggard & P. C. Fletcher (2012) Exploring implicit and explicit aspects of sense of agency. *Conscious Cogn,* 21**,** 1748-53.
Moore, J. W. & S. S. Obhi (2012) Intentional binding and the sense of agency: a review. *Conscious Cogn,* 21**,** 546-61.
Moore, J. W., D. Ruge, D. Wenke, J. Rothwell & P. Haggard (2010a) Disrupting the experience of control in the human brain: pre-supplementary motor area contributes to the sense of agency. *Proc Biol Sci,* 277**,** 2503-9.
Moore, J. W., S. A. Schneider, P. Schwingenschuh, G. Moretto, K. P. Bhatia & P. Haggard (2010b) Dopaminergic medication boosts action-effect binding in Parkinson's disease. *Neuropsychologia,* 48**,** 1125-32.
Moore, J. W., D. M. Wegner & P. Haggard (2009) Modulating the sense of agency with external cues. *Conscious Cogn,* 18**,** 1056-64.
Nachev, P., C. Kennard & M. Husain (2008) Functional role of the supplementary and pre-supplementary motor areas. *Nat Rev Neurosci,* 9**,** 856-69.
Nachev, P., H. Wydell, K. O'neill, M. Husain & C. Kennard (2007) The role of the pre-supplementary motor area in the control of action. *Neuroimage,* 36 Suppl 2**,** T155-63.
Nahab, F. B., P. Kundu, C. Gallea, J. Kakareka, R. Pursley, T. Pohida, N. Miletta, J. Friedman & M. Hallett (2011) The neural processes underlying self-agency. *Cereb Cortex,* 21**,** 48-55.
Nahab, F. B., P. Kundu, C. Maurer, Q. Shen & M. Hallett (2017) Impaired sense of agency in functional movement disorders: An fMRI study. *PLoS One,* 12**,** e0172502.
Neuner, I., C. J. Werner, J. Arrubla, T. Stöcker, C. Ehlen, H. P. Wegener, F. Schneider & N. J. Shah (2014) Imaging the where and when of tic generation and resting state networks in adult Tourette patients. *Front Hum Neurosci,* 8**,** 362.
Oldfield, R. C. (1971) The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia,* 9**,** 97-113.

Pareés, I., H. Brown, A. Nuruki, R. A. Adams, M. Davare, K. P. Bhatia, K. Friston & M. J. Edwards (2014) Loss of sensory attenuation in patients with functional (psychogenic) movement disorders. *Brain,* 137**,** 2916-21.

Pareés, I., T. A. Saifee, P. Kassavetis, M. Kojovic, I. Rubio-Agusti, J. C. Rothwell, K. P. Bhatia & M. J. Edwards (2012) Believing is perceiving: mismatch between self-report and actigraphy in psychogenic tremor. *Brain,* 135**,** 117-23.

Pascual-Leone, A., D. Nguyet, L. G. Cohen, J. P. Brasil-Neto, A. Cammarota & M. Hallett (1995) Modulation of muscle responses evoked by transcranial magnetic stimulation during the acquisition of new fine motor skills. *J Neurophysiol,* 74**,** 1037-45.

Pia, L., M. Neppi-Modona, R. Ricci & A. Berti (2004) The anatomy of anosognosia for hemiplegia: a meta-analysis. *Cortex,* 40**,** 367-77.

Picard, N. & P. L. Strick (2001) Imaging the premotor areas. *Curr Opin Neurobiol,* 11**,** 663-72.

Plomp, G., A. Hervais-Adelman, L. Astolfi & C. M. Michel (2015) Early recurrence and ongoing parietal driving during elementary visual processing. *Sci Rep,* 5**,** 18733.

Preston, C. & R. Newport (2008) Misattribution of movement agency following right parietal TMS. *Soc Cogn Affect Neurosci,* 3**,** 26-32.

Rae, C. L., H. D. Critchley & A. K. Seth (2019) A Bayesian Account of the Sensory-Motor Interactions Underlying Symptoms of Tourette Syndrome. *Front Psychiatry,* 10**,** 29.

Raven, J., J. C. Raven & J. H. Court. 1998. *Manual for Raven's Progressive Matrices and Vocabulary Scales*. San Antonio, TX: Harcourt Assessment.

Renes, R. A., N. E. van Haren, H. Aarts & M. Vink (2015) An exploratory fMRI study into inferences of self-agency. *Soc Cogn Affect Neurosci,* 10**,** 708-12.

Reznik, D., Y. Henkin, O. Levy & R. Mukamel (2015) Perceived loudness of self-generated sounds is differentially modified by expected sound intensity. *PLoS One,* 10**,** e0127651.

Ricciardi, L., P. Haggard, L. de Boer, C. Sorbera, M. P. Stenner, F. Morgante & M. J. Edwards (2017) Acting without being in control: Exploring volition in Parkinson's disease with impulsive compulsive behaviours. *Parkinsonism Relat Disord,* 40**,** 51-57.

Ritterband-Rosenbaum, A., A. N. Karabanov, M. S. Christensen & J. B. Nielsen (2014) 10 Hz rTMS over right parietal cortex alters sense of agency during self-controlled movements. *Front Hum Neurosci,* 8**,** 471.

Rorden, C. & M. Brett (2000) Stereotaxic display of brain lesions. *Behav Neurol,* 12**,** 191-200.

Rossi, S., M. Hallett, P. M. Rossini & A. Pascual-Leone (2011) Screening questionnaire before TMS: an update. *Clin Neurophysiol,* 122**,** 1686.

Rossi, S., M. Hallett, P. M. Rossini, A. Pascual-Leone & S. o. T. C. Group (2009) Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol,* 120**,** 2008-2039.

Saito, N., K. Takahata, H. Yamakado, N. Sawamoto, S. Saito, R. Takahashi, T. Murai & H. Takahashi (2017) Altered awareness of action in Parkinson's disease: evaluations by explicit and implicit measures. *Sci Rep,* 7**,** 8019.

Sato, A. & A. Yasuda (2005) Illusion of sense of self-agency: discrepancy between the predicted and actual sensory consequences of actions modulates the sense of self-agency, but not the sense of self-ownership. *Cognition,* 94**,** 241-55.

Schnell, K., K. Heekeren, R. Schnitker, J. Daumann, J. Weber, V. Hesselmann, W. Möller-Hartmann, A. Thron & E. Gouzoulis-Mayfrank (2007) An fMRI approach to particularize the frontoparietal network for visuomotor action monitoring: Detection of incongruence between test subjects' actions and resulting perceptions. *Neuroimage,* 34**,** 332-41.

Seghezzi, S. & L. Zapparoli (2020) Predicting the Sensory Consequences of Self-Generated Actions: Pre-Supplementary Motor Area as Supra-Modal Hub in the Sense of Agency Experience. *Brain Sci,* 10.

Seghezzi, S., E. Zirone, E. Paulesu & L. Zapparoli (2019) The Brain in (Willed) Action: A Meta-Analytical Comparison of Imaging Studies on Motor Intentionality and Sense of Agency. *Front Psychol,* 10**,** 804.

Shergill, S. S., G. Samson, P. M. Bays, C. D. Frith & D. M. Wolpert (2005) Evidence for sensory prediction deficits in schizophrenia. *Am J Psychiatry,* 162**,** 2384-6.
Shibasaki, H. & M. Hallett (2006) What is the Bereitschaftspotential? *Clin Neurophysiol,* 117**,** 2341-56.
Sidarus, N., M. Vuorre & P. Haggard (2017) How action selection influences the sense of agency: An ERP study. *Neuroimage,* 150**,** 1-13.
Sivak, M., M. J. Flannagan, T. Sato, E. C. Traube & M. Aoki (1994) Reaction times to neon, LED, and fast incandescent brake lamps. *Ergonomics,* 37**,** 989-94.
Spengler, S., D. Y. von Cramon & M. Brass (2009) Was it me or was it you? How the sense of agency originates from ideomotor learning revealed by fMRI. *Neuroimage,* 46**,** 290-8.
Sperduti, M., P. Delaveau, P. Fossati & J. Nadel (2011) Different brain structures related to self- and external-agency attribution: a brief review and meta-analysis. *Brain Struct Funct,* 216**,** 151-7.
Synofzik, M., P. Thier, D. T. Leube, P. Schlotterbeck & A. Lindner (2010) Misattributions of agency in schizophrenia are based on imprecise predictions about the sensory consequences of one's actions. *Brain,* 133**,** 262-71.
Synofzik, M., G. Vosgerau & A. Newen (2008a) Beyond the comparator model: a multifactorial two-step account of agency. *Conscious Cogn,* 17**,** 219-39.
--- (2008b) I move, therefore I am: a new theoretical framework to investigate agency and ownership. *Conscious Cogn,* 17**,** 411-24.
Tremblay, P. & V. L. Gracco (2009) Contribution of the pre-SMA to the production of words and non-speech oral motor gestures, as revealed by repetitive transcranial magnetic stimulation (rTMS). *Brain Res,* 1268**,** 112-24.
Tsakiris, M., M. R. Longo & P. Haggard (2010) Having a body versus moving your body: neural signatures of agency and body-ownership. *Neuropsychologia,* 48**,** 2740-9.
Turkeltaub, P. E., S. B. Eickhoff, A. R. Laird, M. Fox, M. Wiener & P. Fox (2012) Minimizing within-experiment and within-group effects in Activation Likelihood Estimation meta-analyses. *Hum Brain Mapp,* 33**,** 1-13.
Tzourio-Mazoyer, N., B. Landeau, D. Papathanassiou, F. Crivello, O. Etard, N. Delcroix, B. Mazoyer & M. Joliot (2002) Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage,* 15**,** 273-89.
van Buuren, M., T. E. Gladwin, B. B. Zandbelt, R. S. Kahn & M. Vink (2010) Reduced functional coupling in the default-mode network during self-referential processing. *Hum Brain Mapp,* 31**,** 1117-27.
van Kemenade, B. M., B. E. Arikan, T. Kircher & B. Straube (2016) Predicting the sensory consequences of one's own action: First evidence for multisensory facilitation. *Atten Percept Psychophys,* 78**,** 2515-2526.
--- (2017) The angular gyrus is a supramodal comparator area in action-outcome monitoring. *Brain Struct Funct,* 222**,** 3691-3703.
Van Overwalle, F. & K. Baetens (2009) Understanding others' actions and goals by mirror and mentalizing systems: a meta-analysis. *Neuroimage,* 48**,** 564-84.
Voss, M., J. Moore, M. Hauser, J. Gallinat, A. Heinz & P. Haggard (2010) Altered awareness of action in schizophrenia: a specific deficit in predicting action consequences. *Brain,* 133**,** 3104-12.
Vroomen, J. & M. Keetels (2010) Perception of intersensory synchrony: a tutorial review. *Atten Percept Psychophys,* 72**,** 871-84.
Wegner, D. M. (2003) The mind's best trick: how we experience conscious will. *Trends Cogn Sci,* 7**,** 65-69.
Wegner, D. M. & T. Wheatley (1999) Apparent mental causation. Sources of the experience of will. *Am Psychol,* 54**,** 480-92.
Weiss, C., A. Herwig & S. Schütz-Bosbach (2011) The self in social interactions: sensory attenuation of auditory action effects is stronger in interactions with others. *PLoS One,* 6**,** e22723.
Weiss, C., M. Tsakiris, P. Haggard & S. Schütz-Bosbach (2014) Agency in the sensorimotor system and its relation to explicit action awareness. *Neuropsychologia,* 52**,** 82-92.

Wenke, D. & P. Haggard (2009) How voluntary actions modulate time perception. *Exp Brain Res,* 196**,** 311-8.
Wolpe, N., P. Haggard, H. R. Siebner & J. B. Rowe (2013) Cue integration and the perception of action in intentional binding. *Exp Brain Res,* 229**,** 467-74.
Wolpe, N., J. W. Moore, C. L. Rae, T. Rittman, E. Altena, P. Haggard & J. B. Rowe (2014) The medial frontal-prefrontal network for altered awareness and control of action in corticobasal syndrome. *Brain,* 137**,** 208-20.
Wolpe, N. & J. B. Rowe (2014) Beyond the "urge to move": objective measures for the study of agency in the post-Libet era. *Front Hum Neurosci,* 8**,** 450.
Wolpe, N., J. Zhang, C. Nombela, J. N. Ingram, D. M. Wolpert, J. B. Rowe & Cam-CAN (2018) Sensory attenuation in Parkinson's disease is related to disease severity and dopamine dose. *Sci Rep,* 8**,** 15643.
Wolpert, D. M. & Z. Ghahramani (2000) Computational principles of movement neuroscience. *Nat Neurosci,* 3 Suppl**,** 1212-7.
Wolpert, D. M., Z. Ghahramani & M. I. Jordan (1995) An internal model for sensorimotor integration. *Science,* 269**,** 1880-2.
Woods, D. W., J. Piacentini, M. B. Himle & S. Chang (2005) Premonitory Urge for Tics Scale (PUTS): initial psychometric results and examination of the premonitory urge phenomenon in youths with Tic disorders. *J Dev Behav Pediatr,* 26**,** 397-403.
Worsley, K. J. & K. J. Friston (1995) Analysis of fMRI time-series revisited--again. *Neuroimage,* 2**,** 173-81.
Yomogida, Y., M. Sugiura, Y. Sassa, K. Wakusawa, A. Sekiguchi, A. Fukushima, H. Takeuchi, K. Horie, S. Sato & R. Kawashima (2010) The neural basis of agency: an fMRI study. *Neuroimage,* 50**,** 198-207.
Yoshie, M. & P. Haggard (2013) Negative emotional outcomes attenuate sense of agency over voluntary actions. *Curr Biol,* 23**,** 2028-32.
Zapparoli, L., M. Porta & E. Paulesu (2015) The anarchic brain in action: the contribution of task-based fMRI studies to the understanding of Gilles de la Tourette syndrome. *Curr Opin Neurol,* 28**,** 604-11.
Zapparoli, L., S. Seghezzi, F. Devoto, M. Mariano, G. Banfi, M. Porta & E. Paulesu (2020a) Altered sense of agency in Gilles de la Tourette syndrome: behavioural, clinical and functional magnetic resonance imaging findings. *Brain Communications,* 2.
Zapparoli, L., S. Seghezzi & E. Paulesu (2017) The What, the When, and the Whether of Intentional Action in the Brain: A Meta-Analytical Review. *Front Hum Neurosci,* 11**,** 238.
Zapparoli, L., S. Seghezzi, P. Scifo, A. Zerbi, G. Banfi, M. Tettamanti & E. Paulesu (2018) Dissecting the neurofunctional bases of intentional action. *Proc Natl Acad Sci U S A*.
Zapparoli, L., S. Seghezzi, E. Zirone, G. Guidali, M. Tettamanti, G. Banfi, N. Bolognini & E. Paulesu (2020b) How the effects of actions become our own. *Sci Adv,* 6.

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