SAPIENZA
UNIVERSITÀ DI ROMA

Department of Psychology

Electrocortical underpinnings of error monitoring in health and pathology

Candidate: Rachele Pezzetta

FINAL DISSERTATION

International Doctor of Philosophy course in

Psychology and Social Neuroscience

XXXI cycle

Supervisor:

Professor Salvatore Maria Aglioti

Sapienza University of Rome

Reviewers:

Professor Antonino Vallesi

University of Padua

Dr. Giovanni Vecchiato

Consiglio Nazionale delle Ricerche, CNR, Parma

Electrocortical underpinnings of error monitoring in health and pathology

'You must learn from the mistakes of others. You can't possibly live long enough to make them all yourself' [Samuel Levenson, 1911 – 1980 comedian]

Chapter 1 General introduction

'The capacity for cognitive control is perhaps the most distinguishing characteristic of the human behavior […] Understanding the mechanisms that underlie our capacity for cognitive control seems essential to unravelling the mystery of why […] we are capable of intelligent, goal-directed behavior'. [Jonathan D.Cohen, The Wiley Handbook of Cognitive Control, 2017]

The neurophysiology of performance monitoring. What do we mean with 'error'?

The term *error* refers to an event in which action performance fails, and its outcome is worse than expected. A concept strictly related to error is that of associative learning, a mechanism that enables animals and humans to anticipate the occurrence of important events as well as to learn from unsuccessful outcomes how to optimize the behavior. These mechanisms are clearly important from an evolutive perspective (Stout, 2010), but also in everyday life. We can just think of the importance of an adaptive behavior in our daily actions, as when we need to prepare a cup of coffee. The actions to achieve this goal might lead to mistakes. We may have difficulties in opening the moka pot because we are rotating it in the wrong direction, or because we are suddenly distracted by our dog jumping in the kitchen, or again because we forgot the correct steps for preparing a good Italian coffee. In these scenarios it is necessary to detect the wrong behavior and eventually select contextual relevant information for creating future strategies. Indeed, learning arises when the actual outcome differs from the expected one and the brain respond to it, resulting in a prediction error (Kilner, Friston, Frith, 2007; Clark, 2013).

It is then clear how the ability to detect errors in one's own actions, and in the actions of others, is central for flexible behavioral interactions with objects and people (Avenanti, Bolognini, Maravita,

Aglioti, 2007; Cavanagh & Frank, 2014; De Bruijn, Miedl, & Bekkering, 2011; Navarro-Cebrian, Knight, & Kayser, 2013; Ullsperger, Danielmeier, & Jocham, 2014; Panasiti, Porciello, Aglioti, 2017). Convergent evidence derived from studies in humans (Luu, Tucker, & Makeig, 2004; Hajcak, Moser, Yeung, & Simons, 2005) and primates (Tsujimoto, Shimazu, & Isomura, 2006) suggests that the brain communicate the need for control through a network centered upon the frontal regions of the brain (Miller, 2000). According to the detailed review written by Ullsperger and colleagues (2004), the brain structures involved in the process of performance monitoring and adaptive behavior comprise a wide network of frontal areas (i.e posterior medial frontal cortex, pMFC; lateral prefrontal cortex, LPFC; dorsolateral prefrontal cortex, DLPFC), sub-cortical regions, and the cerebellum (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004; Cohen, 2011; Ullsperger, Danielmeier, Jocham, 2014). These regions seem to sub-serve the synergic cooperation between several key functions like perceptual selection, inhibition of responses, programming of goal-directed action, selective attention and online adjustment, collectively referred to as: cognitive control (Botvinick et al., 2001; Ridderinkhof, Van Den Wildenberg, Segalowitz, & Carter, 2004; van Gaal, Ridderinkhof, Fahrenfort, Scholte, & Lamme, 2008; Ambrosini & Vallesi, 2016; Masina, Vallesi, Di Rosa, Semenzato, Mapelli, 2018). A crucial element of cognitive control is the error monitoring function, which operates when the brain detects a deviation of an action from the predicted goal or a conflict between two or more alternatives (Holroyd and Coles, 2002). From all the regions engaged in the performance monitoring, the anterior cingulate cortex (ACC) in particular - with its cytoarchitectonic and functional subdivision - has been largely addressed as a pivotal area involved in error-monitoring (Carter et al., 1998; Switck & Turken, 2002).

Specific electro-cortical markers in the time and time-frequency domains are associated with error monitoring. In the time domain, two cortical potentials are often associated with error processes: Error Related Negativity (ERN) and Error Positivity (Pe). The error processes seem to be highlighted

by specific signatures also in the frequency domain as the theta band (mid-frontal theta; 4-8Hz). A more exhaustive explanation of those markers from a neurophysiological perspective can be found later in the Chapter.

The electrical signatures of error detection (ERN/Pe/mid-frontal theta) have been described in the light of many different frameworks and theoretical models: error significance (Maier & Steinhauser, 2016), cognitive control (Ridderinkhof et al., 2004; Cavanagh & Frank, 2014), reinforcement learning (Holroyd & Coles, 2002; Holroyd, Hajcak, & Larsen, 2006), and rule violation (Krigolson & Holroyd, 2006; Tzur & Berger, 2007). Some studies showed that the mechanism that respond to errors appears to categorize outcomes in a binary manner as events that either do, or do not, indicate that the task goal has been achieved (Hajcak et al., 2005; Janssen, Poljac, & Bekkering, 2016). Other suggested how those signatures follow a graded rather than all-none modulation (Boldt & Yeung, 2015; Spinelli, Tieri, Pavone, Aglioti, 2017). Overall, previous studies suggest that error-related signatures are sensitive to a negative outcome (van Driel, Ridderinkhof, & Cohen, 2012; Wang et al., 2015). However, all these accounts are recently challenged by outcome-prediction interpretations that support valence-free positions, suggesting that error electrophysiological responses are modulated by the likelihood of occurrence related to unexpectedness (Oliveira, McDonald, & Goodman, 2007; Notebaert, Houtman, Van Opstal, Gevers, Fias & Verguts, 2009; Wessel, Klein, Ott, & Ullsperger, 2013) or a wrong prediction (Alexander & Brown, 2012; Hajihosseini & Holroyd, 2013; Donnarumma, Costantini, Ambrosini, Friston, Pezzulo, 2017), rather than the significance of the event itself (as the error significance account; Maier & Steinhauser, 2016).

Neurophysiological signatures in error-monitoring

As said, Electroencephalography (EEG) and Magnetoencephalography (MEG) studies demonstrated how committing an error in a goal-directed action elicits specific electrophysiological correlates.

In the time domain, the Error-related negativity (ERN) or Error Negativity (Ne) was discovered for the first time on errors in speed-response choice tasks (Falkenstein, Hohnsbein, Hoormann, Blanke, 1990; Gehring, Goss, Coles, Meyer, Donchin, 1990). It is a negative deflection peaking at around 80ms after an error is committed (ERN) and reaches its maximal amplitude on FCz and Cz electrodes. If a feedback is provided after an action, a Feedback Related Negativity (FRN) may be observed (Luck & Kappenman, 2011). Both ERN and FRN seem to be associated with the activity of a generic top-down monitoring mechanism (Holroyd & Coles, 2002; Holroyd, Nieuwenhuis, Yeung & Cohen, 2003; Cavanagh, Frank, Klein, & Allen, 2010; Gehring, Liu, Orr, & Carp, 2012; Ullsperger at al., 2014. Ozkan & Pezzetta, 2017). Usually – but not always - the ERN is followed by a positive deflection (Error positivity; Pe) with a diffuse scalp distribution but with maximal amplitude over the central-parietal region of the scalp (Shalgi, Barkan, & Deouell, 2009; Wessel, 2012). This component has many overlapping features with the widely known P300, normally elicited by salient and rare events (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991; Overbeek, Nieuwenhuis, & Ridderinkhof, 2005; Polich, 2007). Whether, on one side, the ERN is believed to reflect an initial and automatic brain response to errors, the Pe appears to be independent from the ERN (Leuthold & Sommer, 1999; De Gregorio et al., 2016) and possibly refers to other aspects of error-processing, such as error awareness, motivational significance, behavioural adaptation or context updating (Nieuwenhuis, Ridderinkhof, Blom, Band, & Kok, 2001; Overbeek et al., 2005).

Interestingly, observing an error committed by others elicits analogous error-related signatures (Miltner, Brauer, Hecht, Trippe, & Coles, 2003; van Schie et al., 2004; Bates, Patel, & Liddle, 2005; Panasiti, Pavone, & Aglioti, 2016). This parallel neural response indicates how observational learning rely on similar neural processes to action execution (van Schie et al., 2004) and may denote an adaptive mechanism that allows to learn from other's behavior and establish effective social interactions (de Bruijn, Miedl, & Bekkering, 2011). A so-called observed ERN (oERN) has been found with similar topographic distribution and neural localization to the ERN, but with a delayed latency (between 50-

400ms compared to the 50-100ms of the ERN). Similarly, also the observed late positivity (oPE) has been reported with overlapping characteristics with the Pe/P300 but with delayed peak amplitude (350-800ms compared to the 100-300ms of the Pe; Koban & Pourtois, 2014).

Recently, typical error signatures of vicarious error processing have also been investigated in a virtual scenario while embodying a fully virtual body in first person perspective (1PP; Padrao et al., 2016) compared to the third person perspective (3PP; Pavone et al., 2016). The term embodiment in virtual reality refers to the sensation of being inside, having and controlling a virtual body (Kilteni, Groten, Slater, 2012). In fact, when a virtual character is embodied in 1PP rather than 3PP (Petkova & Ehrsson, 2008; Slater, Perez-Marcos, Ehrsson, & Sanchez-Vives, 2009) a sensation of Ownership (i.e., the feeling that an artificial agent is part of the body of the observer; Tieri, Tidoni, Pavone, & Aglioti, 2015a**;** Fusaro, Tieri, & Aglioti, 2016) and Agency (i.e., the feeling of being able to control its movement; Tieri, Tidoni, Pavone, & Aglioti, 2015b) are reported. An association was found between the general sensation of embodiment and neural activity, showing how a greater sensation of Embodiment was correlated with greater neural response to observed errors, when those were committed in first person perspective (Pavone et al., 2016).

In the time-frequency domain, error monitoring has been primarily associated with Mid-frontal theta oscillations (4-8Hz; Cohen, 2011; Cavanagh, Zambrano-Vazquez, & Allen, 2012). At a cognitive level, modulations on this frequency range has been often found in paradigms which studied cognitive control, mental effort, and memory performance (Klimesh, 1999; Cavanagh & Frank, 2014). At a neurobiological level, theta has been implicated in synaptic mechanisms of learning, information flow, and inter-regional communication, suggesting entertaining a key role in the brain exchange of information (Fries, 2005; Fries 2015). An increasing number of studies are reporting theta power enhancement or theta synchronization after one commits an error or observe someone else committing a wrong action, as a signal for the need to control (Cohen et al., 2011). The question whether the ERN

might reflect the power increase or phase-locking of theta oscillations is still under debate. Current evidence indeed indicates that ERN activity may be generated from the phase resetting of ongoing theta activity in the prefrontal cortex (PFC) or may originate from a reorganization of ongoing oscillatory neural activity that might begin sometime prior to incorrect responses (Luu et al., 2004; Yeung, Bogacz, Holroyd, Nieuwenhuis & Cohen, 2007). Although over 1000 articles can be found on PubMed when searching 'error-related negativity', much is still unknown about the neural mechanisms that generate this component, as well as its relationship with the responses in the time- frequency domain.

In the error observation literature, there are less clear findings as only a few studies investigated the modulation of oscillatory activity during vicarious error processing (Wang et al., 2015; (Conejero, Guerra, Abundis-Gutirrez, & Rueda, 2016).

Apart from the theta oscillations, which play a primary role in the error monitoring processes, other frequencies have also a been investigated, both in error execution and error observation.

Many studies suggest that motor simulation is a behavioural mechanism crucially involved in attention orienting aimed at understanding the goals of other's actions (Rizzolatti & Craighero, 2004). On this regard, a widely known manifestation of the observational network and the motor simulation process is the alpha (8-12 Hz) suppression among sensorimotor areas (Marshall, & Meltzoff, 2011; Meyer, Braukmann, Stapel, Bekkering, & Hunnius, 2016).

However, the alpha frequency band has also been associated with the general response to infrequent and novel stimuli, that often characterize errors, mainly localized in the posterior electrodes. Posterior alpha activity has in fact extensively been associated to a general reaction to novelty, and in particular with attention orientation to salient conditions (Carp & Compton, 2009; Mazaheri, Nieuwenhuis, Van Dijk, & Jensen, 2009; van Driel et al., 2012; Pavone et al., 2016; Wang et al., 2015). Even if less investigated in this context, also the delta (2-4 Hz) and beta (12-30 Hz) frequency bands seem to play a role in the general processes of performance monitoring. As recently pointed out by

Völker and colleagues (2018), delta activity has been considered a key mechanism in the error monitoring processes and - according to different studies - it has been liked with the generation of ERN/FRN and the Pe (Luu et al., 2004; Yordanova et al., 2004). Concerning the beta frequencies (12/15-30 Hz), not many studies have investigated those signatures in the error monitoring processes. Beta oscillations have usually been found in motor execution/observation tasks, characterized by a beta suppression during the action and post-movement rebound (Pfurtscheller, & da Silva, 1999). However, an interesting MEG study by Koelewijn et al. (2008) tested subjects while engaging in a motor observation task. Results showed that beta oscillations were modulated by the correctness of the observed actions, with greater rebound activity for erroneous rather than correct actions. It is important to underline that - beside their involvement with the observation, imagination and execution of actions - it is still not yet well understood the role of these beta oscillations in the brain, as so their relationship with the correctness of the actions.

Error signatures in aging and pathology and the role of the neurotransmitters

Cognitive control may be malfunctioning with the aging brain (Larson et al., 2016), such as slower brain reaction to errors, greater difficulty of inhibit intrusive and conflicting responses, that might or might not be also associated with reduced ERPs amplitude or reduced frequency power (Vallesi, Stuss, McIntosh, Picton, 2009; Porcaro, Balsters, Mantini, Robertson, & Wenderoth, 2019). However, thanks to compensatory strategies – i.e. overrecuritment of cortical activity or engagement of other brain regions -, the control mechanisms might be still functioning in an adaptive way (Vallesi, McIntosh, Stuss, 2010; Grady, 2012; Kopp, Lange, Howe, Wessel, 2014).

Neurophysiological evidence of alteration in the error-monitoring functioning has been found in patients with psychiatric disorders. Schizophrenic patients for example typically show an aberrant response to errors (Alain, McNeely, Christensen, West, 2002), compared to healthy adults. On the other side, patients with obsessive compulsive disorder (OCD) show an atypical overactivation of the

very same monitoring processes (Endrass et al., 2010). Investigating the functioning of the error monitoring system in psychiatric or neurologic population can help elucidate the complexity of the system itself.

Researches on neurologic patients revealed that people with prefrontal-cingulate lesions had a disrupted processing of error or novel/surprising events (Wessel et al., 2014). Furthermore, patients after traumatic or vascular brain injuries may report altered ability to perform routine gestures (apraxic patients) as well as they may have an impaired awareness of their own deficits – also known as anosognosia -, leading to inability to detect errors in behavior (Canzano et al., 2014). In patients with diagnosis of Apraxia (from the Greek *ἀ- a-* ("without") and *πρᾶξις praxis* (" action")), these deficits cannot be explained by motor/sensory deficits or difficulties in language compression (Zadikoff and Lang, 2005). Apraxia is usually the result of left frontal and parietal lesions, although also cases of apraxia after right brain damage have been reported. Studies showed that patients with lesions in the parietal areas have difficulties in predicting – through motor imagery – the time necessary to perform hand movements, suggesting how that area might be crucial in the storage and/or access of motor representation (Sirigu et al., 1996). In particular, the Ideomotor Apraxia (IA) is a disorder of higher order motor control characterize by the inability to voluntary mime tool use, or imitate gestures after command (Canzano, Scandola, Gobbetto, Moretto, D'Imperio & Moro, 2016). Nowadays, however, no many investigations have been conducted to study the cortical signatures of error monitoring in patients with ideomotor apraxia.

The strict relationship with neurochemical system and performance monitoring is another aspect that attracted the attention of the researchers. In particular, research has been focused on outlining a putative involvement of the dopamine (DA) neurons in the error processing and event coding, both with pharmacological studies on healthy populations, as well as analyses on populations with dopaminergic alterations (Jocham, Klein, & Ullsperger, 2011). Recent studies raised also the attention to a synergic role of other neurotransmitters including serotonine, norepinephrine, GABA

and adenosine, that altogether with the DA, they balance the complex architecture of the performance monitoring system. Concerning the DA, even if its contribution in the performance monitoring system is confirmed by pharmacological and cognitive studies, its precise role is not well understood yet (Jocham & Ullsperger, 2009; Cools & d'Esposito, 2011). At a neurophysiological level, the role of the dopamine is indirectly studied in Parkinson's Disease (PD), a progressive pathology characterized by the degeneration of dopaminergic neurons in the substantia nigra pars compacta, which results in a depletion of dopamine that gradually extends to the limbic and neocortical regions, affecting the functional activity of the fronto-striato-thalamo-cortical circuits in the basal ganglia (Chaudhuri, Healy, & Schapira, 2006; Halliday, & McCann, 2010) and altered diffusion in the frontal lobes, including the supplementary motor area, the presupplementary motor area, and the cingulum (Kendi, Lehericy, Luciana, Ugurbil, & Tuite, 2008). Neuroimaging studies found that PD show an overall loss of gray matter in pre-frontal regions (Biundo et al., 2011) and develop dementia in up to 80% of cases (as attested by longitudinal studies; Aarsland, Zaccai, & Brayne, 2005; Dirnberger & Jahanshahi, 2013). A limited amount of studies has investigated the integrity of the error monitoring in the PD, reporting contrasting results. However, these are only partial results, and nowadays the consequences on the effects of the dopaminergic medication on the cognitive functioning in PD, such as performance monitoring, are not yet understood (Cools & d'Esposito, 2011; Seer, Lange, Georgiev, Jahanshahi, Kopp, 2016).

Outline of the thesis

It becomes clear from the literature described above (Chapter 1), that the error monitoring mechanisms play a fundamental role in signalling the need for cognitive control. Many studies already provided a consistent evidence on the existence of peculiar ways in which the brain signals this need through electrophysiological changes. However, the following set of empirical studies aims to gain

further insight into these complex processes by measuring brain activity changes in situations that alter the way one experience errors.

The second Chapter (Chapter 2) consists of a brief commentary that was made in response to an article on the brain activity to action errors. In this commentary we propose new possibilities to explore our topic of interest, by taking advantage of EEG and modern virtual reality facilities.

The thesis includes three EEG-VR studies: one on the error-mechanism in healthy participants (Chapter 3) and two studies on error monitoring system in pathological populations (Chapter 4, 5), as main parts of the core of the thesis. As a collateral project, in the Appendix, there is an EEG study on action observation in elite players (Chapter 7).

In the first study (Chapter 3), we investigated a very simple but fundamental question. As we saw in the introduction, error-related signatures are evoked when an error occurs. But it is not clear how much of this is due to the occurrence of a violation of the intended goal or simply to the observation of a rare – thus less predictable – event. To this aim, we used a paradigm developed in the former years in our laboratory (Pavone et al., 2016; Spinelli et al., 2017), characterized by a setup in immersive Virtual Reality (VR) and simultaneous EEG recording. Building on the previous findings, we designed an EEG-VR study in which we manipulated the probability of observing errors in actions. In another study (Chapter 4) we investigated how erroneous actions are experienced by people with brain damage and diagnosis of Apraxia. Apraxic patients are people with hemispheric lesions and defective awareness on a variety of aspects that cover perceptuo-motor, cognitive or emotional domains. This study was developed after the results obtained by Canzano and colleagues (2014) in a behavioral study in which apraxic patients were asked to imitate the actions executed by the experimenter and judge their correctness; results revealed that bucco-facial apraxic patients manifest a specific deficit in detecting their own gestural errors when they are explicitly asked to judge them.

With the present study we wanted to investigate apraxic brain' response to action errors, while they embody an avatar in first person perspective (EEG-VR setup).

The third study (Chapter 5) investigates the integrity of the error-monitoring system in Parkinson's Disease and the impact of the dopaminergic treatment in the brain response to errors. To this aim we used the proposed VR action-observation paradigm, in which Parkinson patients observed successful and unsuccessful reach-to-grasp actions in first person perspective while EEG activity was recorded; the same patients were tested while being under dopaminergic treatment and during a dopaminergic withdrawal state.

In another chapter we provide a critical overview of the findings of this work (General Discussion, Chapter 6).

In the last chapter, the Appendix (Chapter 7), there is a collateral project of another research line of the Laboratory, in which I have being involved. In this study we are investigating the cortical underpinning of elite players during observation of goal-directed actions, in their domain of expertise. We recorded the EEG activity of elite wheelchair basketball players while observing free-throws performed by paraplegic athletes. We expected their brain correlates to be different from novice players and to be able to easily discriminate whether a basketball shot would be successful or unsuccessful (project still ongoing).

Starting by the results obtained so far, that are leading us to understand a bit more of the complex architecture of the monitoring system, we are currently performing and designing new experiments, to deeper understand the way our brain processes the world outside and inside us. A brief summary of the ongoing and future studies can be found at the very end of the thesis.

Chapter 2 Predictive monitoring of actions, EEG recordings in virtual reality

Abstract

Predictive monitoring of actions, EEG recordings in virtual reality. J Neurophysiol 119: 1254–1256, 2018. First published December 20, 2017; doi:10.1152/jn.00825.2017. - Error-related negativity (ERN) is a signal that is associated with error detection. Joch and colleagues (Joch M, Hegele M, Maurer H, Müller H, Maurer LK. J Neurophysiol 118: 486–495, 2017) successfully separated the ERN as a response to online prediction error from feedback updates. We discuss the role of ERN in action and suggest insights from virtual reality techniques; we consider the potential benefit of self-evaluation in determining the mechanisms of ERN amplitude; finally, we review the oscillatory activity that has been claimed to accompany ERN.

Keywords: action effect monitoring; ERP; error observation; oscillations; virtual reality.

Error detection is a crucial ability for learning and implementing adaptive behavior. Several MEG/EEG studies have investigated the cortical signatures of error monitoring in a variety of tasks, ranging from the widely known speed-response tasks (i.e., Flanker task, go/no-go) to more finely tuned motor tasks such as grasping an object or hitting a target (Maier et al. 2012; Meyer et al. 2016). EEG studies indicate that execution errors as well as errors of observed action are indexed by specific electrocortical markers in the time and time-frequency do-mains. Specifically, in the time domain, when an error is detected but the result of an action is still explicitly unknown, an error-related negativity (ERN) is observed in the midfrontal regions. Moreover, when the external feedback about the performance is provided, a so-called feedback-related negativity (FRN) is elicited. As the ERN appears before the feedback, it may represent a signal of prediction error. However, this conclusion becomes less straightforward in complex tasks where many other “low level” (action execution related) factors can contribute to the generation of this negative event-related potential. In fact, despite the error prediction process itself, in many studies the participants could still execute corrections while the

action is in progress, or they could visually observe the trajectory that leads to the goal, which makes the contribution of these later factors to the ERN generation unclear. Furthermore, the temporal proximity of any external feedback overlapping with the error detection itself makes it difficult to pinpoint the neural bases of action outcome prediction.

In the target article, when the authors compared the mean amplitude in both the hit and error trials on electrode FCz, they detected a negative deflection between 200 and 350 ms following the ball release for the erroneous trials (ERN). They also found another deflection occurring between 1,000 and 1,200 ms as a reaction to feedback (FRN), also in the midfrontal regions. Whereas in their previous study Maurer et al. (2015) found a broad negative event-related potential (that was interpreted as the neural response to action effect monitoring of the ball flight trajectory), in the target article they observed no significant broad negative deflection in the interval between the ERN and the FRN. Therefore, the aforementioned confound was eliminated in the present work by Joch et al. (2017).

This efficiently verifies that the previously observed negativity was related to the action effect monitoring of the ball flight trajectory. The findings are important because they center on an issue in the error field that focuses on the action observation network (AON), since it involves both visual and proprioceptive information. As this study clarifies, the error signals can indeed continue to be generated due to action effect monitoring; by focusing on what happens in the brain when an action is produced before any immediate external feedback (as the ball trajectory represents), one is able to focus on the prediction of an error based on the pure action kinematics. When an action is observed (visual), the preexisting sensorimotor network (AON) is engaged, especially more robustly when the observed action is familiar. In a way, this resembles the information from the "memory" of a proprioceptive component of the very same action. Thus, if an individual is executing an action while observing the consequence visually, but not observing the outcome, it is possible to narrow the window in which the error signal occurs. Below we discuss how this quasi-virtual paradigm and the results pave the way to find out the fine nuances of error detection and even the prediction of an error.

We have three points to make about the implications of this study and the further opportunities it presents.

First, the target article paradigm emphasizes the distinction on whether the error signal codes the error prediction itself or the knowledge that an error has happened or whether it is a more general signal that occurs in both types of situations. Tellingly, the study is embedded in the context of the forward model of action prediction, which comprises the efferent in-formation derived from the muscles and the afferent information from the action trajectory. According to the forward model, a prediction is generated by integrating available sources. In this paradigm, the informative sources are *1*) the throwing movement, which produces an efference copy, and *2*) the visual and proprioceptive online information about the very same movement (Aglioti et al. 2008). Specifically, in the target article, the efferent copy is represented by the lever press (release of the ball), but it is still coupled with the observed trajectory until the movement of the press ends, even though the following observation is prevented. Therefore, as mentioned by the authors themselves, the online sensory in-formation here is both visual and proprioceptive. There are several ways to approach the issue, building on the target article. The intention to separate the efferent and afferent copies of error prediction lead us to propose an alternative use of the augmented reality techniques, coupled with motion tracking (for a similar paradigm, see Yazmir and Reiner 2016). With a motion tracking system (e.g., cyber gloves), it is possible to carry the movement of hands to the virtual environment without the need to utilize a lever as an intermediary apparatus. If the real-time movement can be translated into a virtual environment in another sensory prediction task, the visual cues from the virtual environment can be manipulated to create a scenario in which sensory information can be congruent with visual information and where the visual information is unavailable after the movement itself is learned by heart (similarly applications on animal studies, such as in Schwartz et al. 2004). In the unavailable visual information condition, it would be possible to observe whether there is a point in which the participants can detect their executed error. Thus, the pure effect of proprioceptive information on error

detection can be separated from the visual information that relates to the AON. By means of virtual reality, strong control over the environment and reliable sensory information can be obtained and new discoveries can be made regarding cortical signatures of error prediction in adaptation, such as in the cases of expertise, where the absence of efference copy (by means of a paradigm similar to the target article's) is easily compensated due to the simulated action based on the learned domain-specific kinematics (Aglioti et al. 2008).

Second, the ERN reported by Joch et al. (2017) had a later latency and smaller amplitude compared with choice-reaction time tasks. The authors explain that task complexity leads to less accurate predictions. Collecting confidence ratings before the external feedback could also help address this issue. Di Gregorio et al. (2016) proposed a paradigm in which participants respond with one of the three options in a visual-color matching task. Each response was followed by a self-evaluation of performance: participants judged whether the response provided was correct or incorrect and, if incorrect, indicated which of the wrong targets they responded to. This allowed the authors to sort trials by the level of confidence on error commission and disentangle implicit and explicit correctness of the predictions. From the neuroelectrical point of view, this confidence about the prediction, and thus the level of aware-ness about the performed action, was previously linked to the error positivity (Pe, a positive signal that peaks approx. 100 –200 ms after an error) (Ridderinkhof et al. 2009). We think that in future research findings regarding a late positivity after ERN or FRN would clarify this point. This can create an informative picture of predictive processes and confirm whether the certainty of error prediction and the amplitude of ERN covary with the Pe or whether the two mechanisms underlying the two cortical potentials are independent.

Lastly, aside from the evidence based on ERPs, a growing literature based on time-frequency domain analyses reveal interesting results on the link between error prediction processes and brain oscillatory activity. For future research, we think that the current paradigm is well suited for analysis that aims to separate the phase-locked and non-phase-locked features of the theta-band activity, which may be

related to the ongoing events after an action. It is important to recognize that ERP components have a complex heterogeneous structure composed of frequency-specific oscillations (Yordanova et al. 2012). In the time-frequency domain, delta (2-4 Hz) together with frontal midline theta (4-8 Hz) has been considered a key mechanism in the generation of ERN and FRN. Moreover, extensive literature support theta involvement in behavioral and cognitive control (Cavanagh et al. 2009; Luu et al. 2004), so the oscillatory theta activity may be a consistent neurophysiologic marker of the mismatch (error) information by the monitoring system.

To conclude, the elegant paradigm in the target paper temporally localizes the action related ERN by obscuring the visual action effect monitoring and delaying the feedback. The authors' paradigm and similar motor tasks could provide fruitful opportunities to disentangle the neuroelectrical patterns of error prediction processes in controlled virtual environments. The mentioned ERPs and the related oscillatory activity are useful to understand the neuropsychological mechanisms for coordinating different cognitive processes involved in predictive processes.

Chapter 3 Error, rather than its probability, elicits specific electrocortical signatures: a combined EEG immersive virtual reality study of action observation

'Experience is the name everyone gives to their mistakes'
[Oscar Wilde 'Lady Windermere's Fan', 1892]

And… in more recent years ...

'The predictive brain may often function as a stubborn, rather than idealised scientist, failing to update predictions on the basis of sensory evidence'
[Yon, de Lange, & Press, Trends in Cognitive Science, 2018]

Abstract

Detecting errors in one's own actions, and in the actions of others, is a crucial ability for adaptable and flexible behavior. Studies show that specific EEG signatures underpin the monitoring of observed erroneous actions (error-related negativity, error positivity, mid-frontal theta oscillations). However, the majority of studies on action observation used sequences of trials where erroneous actions were less frequent than correct actions. Therefore, it was not possible to disentangle whether the activation of the performance monitoring system was due to an error, as a violation of the intended goal, or to a surprise/novelty effect, associated with a rare and unexpected event. Combining EEG and immersive virtual reality (IVR-CAVE system), we recorded the neural signal of 25 young adults who observed, in first-person perspective, simple reach-to grasp actions performed by an avatar aiming for a glass. Importantly, the proportion of erroneous actions was higher than correct actions. Results showed that the observation of erroneous actions elicits the typical electrocortical signatures of error monitoring, and therefore the violation of the action goal is still perceived as a salient event. The observation of correct actions elicited stronger alpha suppression. This confirmed the role of the alpha-frequency band in the general orienting response to novel and infrequent stimuli. Our data provide novel evidence that an observed goal error (the action slip) triggers the activity of the performance-monitoring system even when erroneous actions, which are, typically, relevant events, occur more often than correct actions and thus are not salient because of their rarity.

NEW & NOTEWORTHY Activation of the performance-monitoring system (PMS) is typically investigated when errors in a sequence are comparatively rare. However, whether the PMS is activated by errors per se or by their infrequency is not known. Combining EEG-virtual reality techniques, we found that observing frequent (70%) action errors performed by avatars elicits electrocortical error signatures suggesting that deviation from the prediction of how learned actions should correctly deploy, rather than its frequency, is coded in the PMS.

Introduction

Detecting errors in one's own actions, and in the actions of others, is a crucial ability for flexible behavioral interactions with objects and people (Avenanti et al. 2007; Cavanagh and Frank 2014; de Bruijn et al. 2011; Navarro-Cebrian et al. 2016; Panasiti et al. 2017; Ullsperger et al. 2014a). Studies in humans (Hajcak et al. 2005; Luu et al. 2004) and nonhuman primates (Tsujimoto et al. 2006) have shown that the monitoring of erroneous actions triggers specific EEG signatures that index neural activity in a network centered on the middle-frontal regions (Cohen, MX, 2004b; Cohen, MX, 2011; Ridderinkhof et al. 2004). Crucially, performance-monitoring signatures are elicited by committed and observed errors, which suggests the presence of a fundamental, adaptive mechanism that detects the deviation of an action from the predicted goal (Joch et al. 2017; van Schie et al. 2004). This mechanism is particularly relevant in sports (Abreu et al. 2012; Aglioti et al. 2008; Makris and Urgesi 2014; Proverbio et al. 2012; van Pelt et al. 2016) and music performances (Candidi et al. 2014; Panasiti et al. 2016), two domains that require fast detection of salient information. In the time domain, two event-related potentials (ERPs) have been extensively linked to error monitoring, namely, error-related negativity (ERN) and error positivity (Pe). The ERN is a negative deflection peaking around 80 ms after an error is committed (Luck and Kappenman 2011). The Pe is a sustained positive deflection that typically follows the ERN, with a diffuse distribution but with maximal amplitude over the central-parietal region of the scalp (Shalgi et al. 2009; Wessel et al., 2012). The

Pe has many overlapping features with the widely known P300 (Overbeek et al. 2005; Ridderinkhof et al. 2009). In addition to the morphology and the scalp distribution, both components are elicited in response to task-significant stimuli (e.g., low-probability targets) (Gehring et al. 2012; Overbeek et al. 2005; Polich 2007). However, the Pe has an additional property in that it reflects the motivational significance of a salient performance error (Ridderinkhof et al. 2009). In fact, whereas the ERN is believed to reflect an initial and automatic brain response to an error, the Pe likely reflects higher levels of error processing, such as error awareness, reorientation of the attention, behavioral adaptation, or context updating (Nieuwenhuis et al. 2001; Ridderinkhof et al. 2009). The ERN and the Pe appear to be two mechanisms that might be independent (Di Gregorio et al. 2016) and that characterize the complex performance monitoring system. In the time-frequency domain, error monitoring has been primarily associated with mid-frontal theta oscillations (4–8 Hz) that appear to increase when an error is committed (Cavanagh and Frank 2014; Cavanagh et al. 2012; Cohen 2011). Although a study suggested that ERN and theta activity are functionally linked and that the former may originate, at least partially, from the phase-locking of the latter (Luu et al., 2004), recent data simulations contradict this idea (Yeung et al. 2007). Another frequency band engaged in the general response to infrequent and novel stimuli, a property that often characterizes errors, is the alpha activity. The decreased power in this frequency band (generally 8–12 Hz) is often linked to the physiological reaction to novelty and the orientation effect toward salient conditions. This modulation of power in alpha activity has been found mainly in the middle-central (Pavone et al. 2016; Wang et al. 2015) and middle-posterior electrodes/sensors (Carp and Compton 2009; Mazaheri et al. 2009; van Driel et al. 2012). Whereas the original EEG characterization of the error monitoring system has been studied in relation to performed errors (Falkenstein et al. 1991; Gehring et al. 1993), subsequent studies also indicate that the detection of errors in the actions of others is indexed by specific electrocortical signatures, as well (Bates et al. 2005; Miltner et al. 2004; Panasiti et al. 2016; van Schie et al. 2004). In particular, studies report that the so-called observed ERN (oERN) and observed error positivity (oPe) have a topographic distribution and neural localization similar to the ERN and

Pe, respectively. However, the observation-related error-monitoring components exhibit smaller amplitude and delayed latency with respect to the execution-related components (Koban and Pourtois 2014; Koban et al. 2010; van Schie et al. 2004). The link between markers of error execution and observation in the time-frequency domain is less clear, because only a limited number of studies have investigated the modulation of oscillatory activity during vicarious error processing (Conejero et al. 2018; Pavone et al. 2016; Spinelli et al. 2018; Wang et al. 2015). In both error-execution and error-observation literature, error-related potentials and frontal midline theta activity have been associated with error significance (Maier and Steinhauser 2016; Nieuwenhuis et al. 2007), cognitive control (Cavanagh and Frank 2014; Cavanagh et al. 2009; Corbetta and Shulman 2002; Wokke et al. 2017), reinforcement learning (Holroyd and Coles 2002; Holroyd et al. 2006; Volpato et al. 2016), and rule violation (Arrighi et al. 2016; Krigolson and Holroyd 2006; Tzur and Berger 2007). Although certain studies suggest that error-related signatures are sensitive to outcome significance (van Driel et al. 2012; Wang et al. 2015), outcome-prediction accounts support valence-free interpretations. According to those accounts, error-related cortical responses are modulated by the likelihood of occurrence and its link with unexpectedness (Garofalo et al. 2017; Notebaert et al. 2009; Núñez Castellar et al. 2010; Oliveira et al. 2007; Wessel et al. 2014). Thus, a wrong prediction (Alexander and Brown 2011; Donnarumma et al. 2017; Hajihosseini and Holroyd 2013; Kilner et al. 2007), rather than the significance of the event itself (Maier and Steinhauser 2016; Maier et al. 2012), may account for the triggering of error-related signatures. To date, most research on action execution and observation has relied on tasks where error trials were the most infrequent events (Bates et al. 2005; Conejero et al. 2018; Miltner et al. 2004; Pavone et al. 2016; van Schie et al. 2004). This type of design makes it impossible to discern whether ERN amplitude and theta power are modulated by the goal violation or by the fact that the error is a rare event in a series. It is worth noting that error observation studies in which the same number of correct and erroneous actions were used did not find an oERN (de Bruijn et al. 2007; Panasiti et al. 2016) or found contrasting results (de Bruijn and von Rhein 2012; Kobza and Bellebaum 2013; Padrao et al. 2016; Wang et al. 2015). Also, most of the

previous studies were based on a speed-response choice task (Koelewijn et al. 2008; van Schie et al. 2004), and observed action errors were coded with respect to sequential frame pictures (de Bruijn et al. 2007) and thus considered as all-or-none events. In a minority of studies focused on continuous motor actions (Bekkering et al. 2009; Meyer et al. 2016), no analyses on error signals were provided. However, in the circumstances of daily life, actions and action errors occur along a continuum, because the environment requires us to constantly monitor and detect crucial information, often in the absence of explicit feedback about the instant at which the error is coded. To deal with such issues, we designed an EEG-immersive virtual reality task in which healthy participants observed an avatar perform successful (correct) or ineffective (erroneous) reach-to-grasp actions involving a glass. At variance with Pavone et al. (2016) and Spinelli et al. (2018), we reversed the proportion of erroneous trials. This meant that erroneous actions were the most frequent event (70% of cases) and that a successful grasp was rarely observed (30% of cases). This difference allowed us to disentangle the contribution error per se, rather than its rarity, in modulating the activity of the human performance monitoring system, and specifically in detecting errors in the continuous actions of a virtual agent.

Finding greater ERN amplitude and greater oscillatory activity in theta after an erroneous action would suggest that these electrical events signal the detection of an error (as a divergent event compared with the intended goal) independently from its frequency. By contrast, finding increased ERN and theta power after correct actions would suggest that these electrical correlates code for rare, and thus less expected events. On the basis of the possible link between rare stimuli and alpha modulation, we predicted stronger parietal-occipital alpha suppression in the correct, less frequent outcome.

Methods and Materials

Participants

Twenty-five participants (one left-handed) took part in the experiment. They had normal or corrected-to-normal visual acuity and reported no history of neurological or psychiatric diseases. All participants were naive as to the purposes of the experiment, signed the written informed consent, and received a compensation of €7.5 per hour. The experimental protocol was approved by the local Ethics Committee at the Fondazione Santa Lucia Research Hospital (Rome, Italy) and was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki. Data from two participants were discarded because of technical reasons; therefore, EEG analyses were conducted on a total sample of 23 participants (14 women; age: 25.22 ± SD 3.02 yr., mean ± SD). The appropriateness of our sample sizes was established using G*Power software (Faul et al. 2007), which indicated that 20 participants would be required to detect a medium effect with a power of 0.8 at an alpha of 0.05.

Apparatus, Stimuli, and Procedure

Participants sat in a cave automatic virtual environment (CAVE) with projectors directed to four walls of a room-sized cube (3m X 3 m X 2.5 m; Cruz-Neira et al. 1993). The virtual scenario consisted of a basic room with a table. At the center of the table, a yellow parallelepipedon was located with a blue glass on top of it. Participants observed one avatar in first-person perspective (1PP; see Fig. 1) seated on a chair in front of a table with its arms resting on the table. The glass was placed in the avatar's peripersonal space at a distance of ~50 cm (Costantini et al. 2011). The avatar and the scenarios were created by means of Autodesk Maya 2011 and 3D Studio Max 2011, respectively. The kinematics of the avatar were implemented by HALCA library (Gillies and Spanlang 2010), and the experiment was performed in an immersive three-dimensional (3D) virtual environment with a real-size avatar drawn on a 1:1 scale and rendered in XVR 2.1 (Huang et al. 2013; Tecchia et al. 2014). Participants wore Nvidia stereo glasses in which 3D virtual images were alternately displayed on both eyes with a refresh rate of 60 Hz. Moreover, these stereo glasses were

interfaced with an Intersense 900 ultrasonic system (Thales Visionix) and constantly tracked the head position during the experiment.

Experimental Procedure

Before the beginning of the experiment, participants underwent a familiarization phase with the experimental setup, as well as a calibration phase within the virtual environment, which consisted of adapting the size of the virtual body to the real one. After this phase, a brief practice session (8 trials, 4 correct and 4 erroneous) occurred. Each participant was informed that the goal of the avatar's movements was to reach and grasp the glass on the table and that the action might or might not be successful. The total number of trials per participant was 100, 70 of which were incorrect and 30 of which were correct. This is the same number of trials used in Pavone et al. (2016) but with the inverse proportion (70 correct and 30 incorrect). The total duration of our experiment was ~20 min. Participants were not informed about the probability of the different action outcome. At the onset of each trial, a sound signaled the beginning of the action. During the trial, participants observed the movement of the avatar's right arm in 1PP. The kinematics of the movement were identical for the first 700 ms in both conditions and began to diverge in the last 300 ms. The trajectory deviation led to either a successful or unsuccessful grasp. The deviation from the to-be grasped object was identical in all the erroneous trials (Fig. 1). The sequence of correct and incorrect trials was randomized. After the end of the action, the avatar's arm rested for 1,000 ms (± 50 ms) before a black screen appeared. During the intertrial interval (ITI), three different situations could occur: 1) in 10% of the trials, participants had to answer a catch question ("Did the arm take the glass?" (yes/no answer); 2) in 40% of the trials, an empty black screen was presented; and 3) in 50% of the trials, participants had to provide ratings concerning the sense of embodiment. When the first and third cases occurred, the black screen lasted until a vocal response was given, whereas when the second case occurred, the experimenter pressed a key to start the next trial, producing a variable ITI (mean duration: ~4,000 ms). To measure their sense of embodiment, participants were asked to verbally rate two questions

on a visual analog scale (VAS) from 0 to 100. One question was about their sense of ownership ("To what extent did you feel the arm was yours?"; 0 = no ownership to 100 = maximal ownership; Slater et al. 2010), and the other question was about their sense of agency ("How much did you feel in control of the arm?"; 0 = no control to 100 = maximal control; Fusaro et al. 2016; Tieri et al. 2015a, 2015b; Villa et al. 2018). The two questions were always presented together and in a randomized order. A total of 819 embodiment ratings for erroneous trials, and 351 embodiment ratings for correct trials, were collected across the whole sample, with each embodiment rating including the two questions on ownership and agency (2 participant ratings were missing due to technical issues during the saving of data and therefore were not included; 21 participants responded to the VAS in 50% of trials, and 4 responded to it in 30% of trials).

Statistical analyses were done using R software (R Core Team 2014). ERPs and time-frequency analyses were made using the erpR package (Arcara and Petrova 2014). All ANOVAs were performed using the ez package (Lawrence 2013). Analyses were performed using repeated-measures ANOVA, and Greenhouse-Geisser correction for nonsphericity was applied when appropriate. By estimating the effect size relative to the ANOVA test, we report the partial eta squared ($\eta 2p$). Spearman correlations were executed, and Bonferroni corrections for multiple comparisons were applied when necessary. Practice trials were excluded from the analyses.

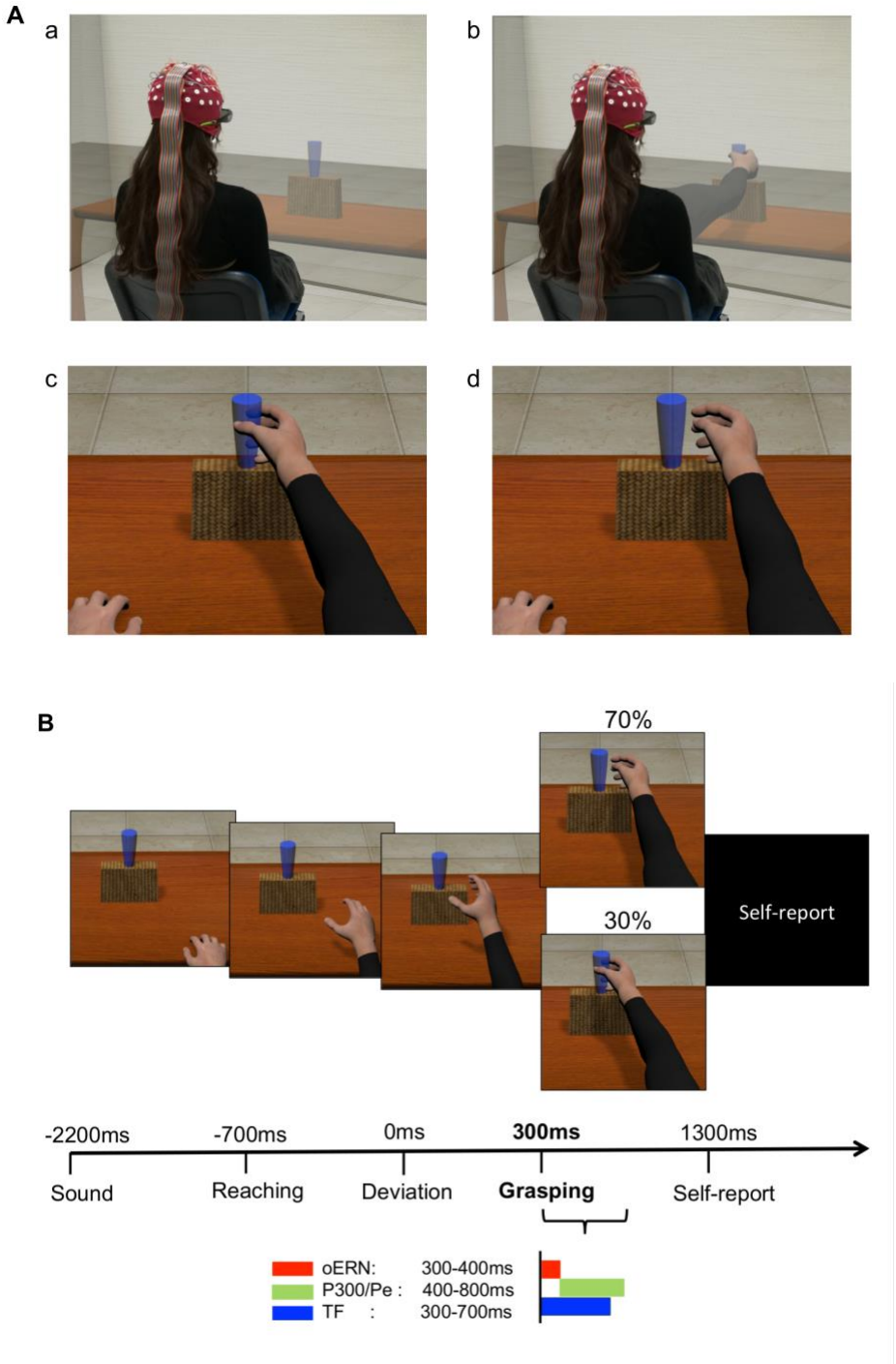


Figure 1. A: example of the experimental paradigm and setup. Top images show the participant in the 3-dimensional (3D) rendering of the virtual scenario (cave automatic virtual environment, CAVE), during which projectors are directed to the 4 walls of a room-sized cube; the participant observes a static situation before the beginning of the trial (a) and at the end of an action (b). Bottom images represent a snapshot from inside the CAVE. The participant is immersed in the virtual scenario. In first-person perspective, using 3D visualization glasses, the participant observes a real-size avatar's arm, perceived as attached to the shoulder during a correct (c) and an erroneous (d) grasping. B: timeline of a single trial. The avatar's action lasted 1,000 ms: the reaching

phase was equal for both types of movements and lasted 700 ms; the deviation phase in which the avatar's arm-path deviation could occur and define an erroneous or correct action lasted 300 ms. The onset of the avatar's limb-path deviation is set at 0 ms; the end of the avatar's action occurs at 300 ms. The main EEG analyses (reported at bottom) have been conducted with intervals of interest chosen a priori. oERN, observed error-related negativity; P300/Pe, error positivity; TF, window of time-frequency analysis.

EEG Recording and Preprocessing Analysis

EEG signals were recorded using a Neuroscan SynAmps RT amplifier system and 60 scalp electrodes embedded in a fabric cap (Electro-Cap International), arranged according to the international 10–10 system[1]. Horizontal electro-oculogram was recorded bipolarly from electrodes placed on the outer canthi of each eye. EEG signal was recorded continuously in alternating current mode with a bandpass filter (0.05–200 Hz) and sampling rates of 1,000 Hz. Impedances were kept under 5 k. All electrodes were physically referenced to an electrode placed on the right earlobe and re-referenced offline to the average of both earlobe electrodes. Offline, raw data were low-pass filtered with a 40-Hz filter (finite impulse response filter, transition 40–42 Hz, stopband attenuation 60 dB). For ERP analyses, an additional bandpass filter (0.5–30 Hz) was applied on the continuous raw signal. Independent component analysis (ICA; Jung et al. 2000) was performed on the continuous EEG signal while components that were clearly related to blinks and ocular artifacts were removed (on average, 3.4 ICA components; range 2–5). EEG signal was then downsampled to 500 Hz and epoched in wide windows of 3-s length, from -1.5 to +1.5 s to avoid edge artifacts induced by the following wavelet convolution. Epochs were time-locked to the onset of the avatar's arm-path deviation, (i.e., 700 ms from the beginning of the movement, as in Spinelli et al. 2018). All epochs were baseline corrected to the 200 ms preceding the avatar's arm-path deviation (i.e., when the limb movements were identical in correct and incorrect conditions; Pavone et al. 2016). The offset of the

[1] The EEG was recorded from the following channels: Fp1, Fpz, Fp2, AF3, AF4, F7, F5, F3, F1, Fz, F2, F4, F6, F8, FC5, FC3, FC1, FCz, FC2, FC4, FC6, T7, C5, C3, C1, Cz, C2, C4, C6, T8, TP7, CP5, CP3, CP1, CPz, CP2, CP4, CP6, TP8, P7, P5, P3, P1, Pz, P2, P4, P6, P8, PO7, PO3, AF7, POz, AF8, PO4, PO8, O1, Oz, O2, FT7, and FT8.

avatar's movement occurred 300 ms after the avatar's limb deviation began. Each epoch was then visually inspected for artifacts to manually remove residual eye blinks or epochs exceeding -100/+100 μV amplitude. A total of 1,524 erroneous trials and 665 correct trials were analyzed for both ERPs and time-frequency analyses (~96% of total collected trials). Because the correct and incorrect actions had different occurrence rates (70% vs 30%), we selected the trials from the incorrect condition to keep the number of trials equal in the two conditions and avoid spurious effects due to the different signal-to-noise ratios (Cohen 2014a; Luck 2005). Therefore, for each participant, trials from the incorrect condition were selected with a built-in Brainstorm function that selects a subset of trials[2]. The main findings, with the total amount of incorrect trials, are reported in *RESULTS, EEG Analyses on All the Incorrect Trials*. Bad channels were replaced using the spherical splines method only when necessary (4 channels were interpolated in only 1 subject; Perrin et al. 1989). Analyses were performed using the Brainstorm toolbox (free open source for MEG/EEG analysis, https://neuroimage.usc.edu/brainstorm/; Tadel et al. 2011) and customized MATLAB routines (Cohen 2014a).

Analysis in the Time Domain: Action Observation-Related ERPs

In line with the literature, oERN and oPe/P300 were respectively analyzed on FCz and Pz electrodes, where they reached their maximum amplitude. The oERN was analyzed in the 100-ms time window following the end of the avatar's action (300–400 ms) at FCz electrode. The oPe/P300 were measured in a preselected time window between 400 and 800 ms at the parietal sites (Pz), in line with previous results (Pavone et al. 2016). All ERPs analyses were based on mean amplitude (Luck 2005). Widely recognized in error literature, the ERN can be hidden from the massive contribution of error positivity components that propagate from parietal to frontal areas and that mask some of the frontal components (Luck 2005). For visualization purposes, we minimalized overlap

[2] In Brainstorm, this is accomplished with the process "File Select Subset- Uniformly distributed." This selection is based on the following MATLAB command: [round (linspace (1, Number_of_erroneous_trials, n_30_selected trials))].

between different components (Fig. 2A) by computing the difference waves in which the average number of correct trials is subtracted from the average number of erroneous trial (Fischer et al. 2017; Koban et al. 2010; Maier and Steinhauser 2016).

Analysis in the Time-Frequency Domain

For the time-frequency analysis, we used a complex Morlet transformation to compute time-frequency decomposition. A mother wavelet with central frequency of 1 Hz and 3 s of time resolution (full width half maximum, FWHM) was designed as in Brainstorm software (Tadel et al. 2011) The other wavelets were computed from this mother wavelet and ranged from 1 to 30 Hz, with 0.5-Hz linear frequency steps. To normalize each signal and frequency bin separately with respect to a baseline, we computed the relative power change (in %) over the time-frequency decomposition as:

$$F = \frac{\mathrm{S(t,f)} - \mathrm{Sbase\ (t,f)}}{\mathrm{Sbase(t,f)}} * 100$$

where S(t, f) is the signal spectrum at a certain given interval of time (t) and frequency (f), and S_{base}(t, f) represents the signal power of the reference signal used as baseline. To avoid edge effects, the power activity from -250 to -50 ms, a window in which the avatar's movement was identical in erroneous and correct conditions, was used as the baseline interval. Positive and negative values index a decrease or an increase in synchrony of the recorded neuronal population (Pfurtscheller and Lopes da Silva 1999) with respect to a given reference interval, where equal neural activity is expected between conditions. In our case, a relative power increase/decrease represents a modulation of power compared with the mean power activity during the baseline. As in Pavone et al. (2016), the main analyses were computed on FCz electrode, focusing on theta (4–8 Hz), alpha (8 –12 Hz), and beta (13–30 Hz) bands, and in the preselected time interval from 300 to 700 ms (i.e., in time windows of 400 ms from the end of the avatar's action). On theta frequency, we also performed the analyses on POz electrode to rule out the possibility of a more general, rather than a mainly frontal, effect (Pavone

et al. 2016). Further exploratory analyses were also performed. To check whether the participants consciously perceived the error before the end of the action, we analyzed theta activity in the time range of action divergence before the outcome appeared (0–300 ms). It is widely held that evoked oscillations reflect a phase-locked activity to the stimulus in the time frequency activity. To investigate whether the reported theta effect is a different representation of the oERN in the time domain, we performed an additional analysis in which we removed the evoked response from each trial before computing the time-frequency decomposition for both experimental conditions.

Results

Time Domain Analysis

oERN

Analyses on oERN revealed a main effect of Condition [$F(1,22)= 6.77$, $p=0.016$, $\eta^2=0.24$], with erroneous actions showing less positive values than correct actions [mean value in erroneous condition ($M_{ERR)}$ =1.76 μV; mean value in correct condition (M_{CORR}) =3.54 μV] (Figure 2A). The topographical distribution shows the typical fronto-central negativity (Figure 2B).

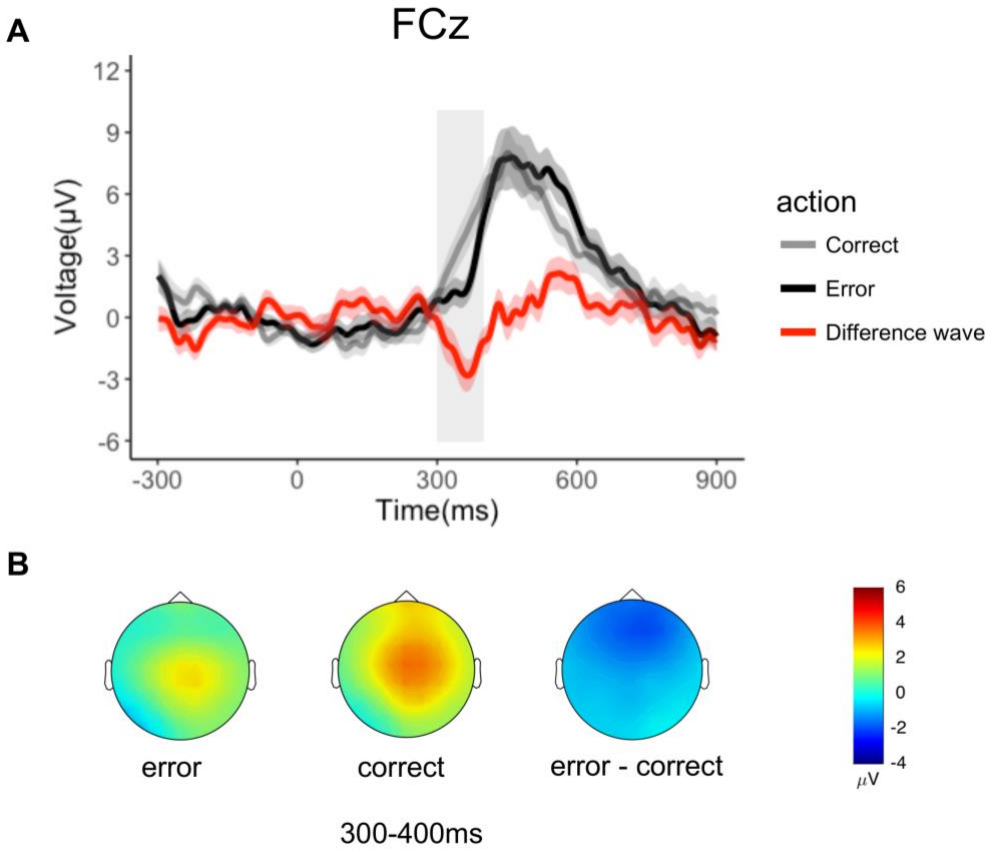


Figure 2 Electrophysiological results in the time domain for each condition (70% erroneous actions, 30% correct actions). **A.** Grand average waveforms of oERN at electrode FCz, over an interval of interest (300-400ms) chosen a priori. The onset of avatar's limb-path deviation is at 0ms; the end of avatar's action occurs at 300ms. Shaded areas denote the standard error around the mean. The grey rectangle highlights the time window considered for statistical analysis. For representation purposes we computed the difference wave on FCz, showing the negative amplitude of the oERN. **B.** Topographical voltage distribution for erroneous, correct and erroneous-minus correct action condition.

oPe

Analyses on oPe revealed that the main effect of Correctness between the two conditions was not significant [$F_{(1,22)}$= 0.25, p= 0.62, η^2= 0.01, M_{ERR}= 5.48μV; M_{CORR}= 5.22μV; Fig. 3A]. Figure 3B shows the typical topographical distribution of oPe over centroparietal recording sites, for both correct and erroneous actions.

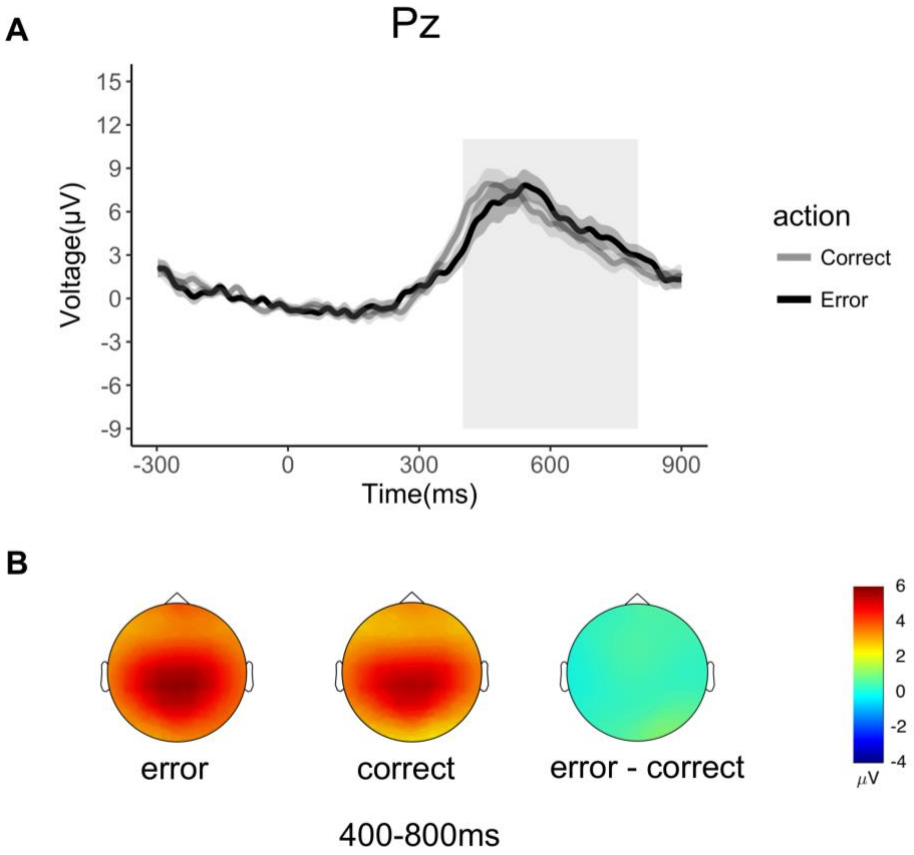


Figure 3. Electrophysiological results in the time domain for each condition (70% erroneous actions, 30% correct actions). **A.** Grand average waveforms of oPe at electrode Pz on an interval of interest (400-800ms) chosen a priori. The onset of avatar's limb-path deviation is at 0ms; the end of avatar's action occurs at 300ms. Shaded areas denote the standard error around the mean. The grey rectangle highlights the time window considered for statistical analysis. **B.** Topographical voltage distribution for erroneous, correct and erroneous-minus action condition.

Time-frequency results

Theta (4-8Hz)

ANOVA on the electrode and time interval of interest showed a significant effect of Condition [$F_{(22,1)}$=18.35; p<0.005, η^2=0.45] with higher theta power activity for observation of erroneous actions compared to correct actions [M_{ERR}=7.18; M_{CORR}=-8.11] (Figure 4; figure 5). A middle-frontal cluster (FCz, FC1, FC2, Fz, F1, F2) revealed a wide frontal distribution [$F_{(22,1)}$=17.48; p<0.05, η^2=0.44],

confirming the greater theta activity in the erroneous rather than correct actions [M_{ERR}= 8.33; M_{CORR}= -6.44]. The same ANOVA on POz showed no significant difference concerning the accuracy of the grasp [$F_{(22,1)}$=3.34; p=0.08, η^2=0.13]. The time interval between the zero-onset and the end of the avatar's movement (0-300ms) showed no significant difference [$F_{(22,1)}$= 1.98; p=0.17, η^2=0.08]. With the removed evoked activity – obtained by removing trial by trial the evoked activity from the total activity before the grand average -, the analysis of the theta activity showed a significant effect of Condition [$F_{(22,1)}$= 17.15; p<0.005, η^2=0.44]: higher theta power activity was shown for observation of erroneous actions compared to correct actions.

Alpha (8-12 Hz)

ANOVA on FCz in the 300-700ms showed a main significant effect of Condition [$F_{(22,1)}$=11. 08; p<0.005, η^2=0.34]. This effect was associated with increased alpha power for erroneous actions and decreased alpha power for correct actions [M_{ERR}=5.36; M_{CORR}=-12.92] (Fig.4). Analyses on POz revealed a consistent alpha suppression [$F_{(22,1)}$= 10.09; p<0.005, η^2=0.31] in the posterior electrode during the correct actions, rather than the erroneous [M_{ERR}= -3.48; M_{CORR}= -23.70] (Fig.5).

Beta (12-30Hz)

No significant main effect or interactions were found for this band [$F_{(22,1)}$= 0.47; p=0.50, η^2=0.02].

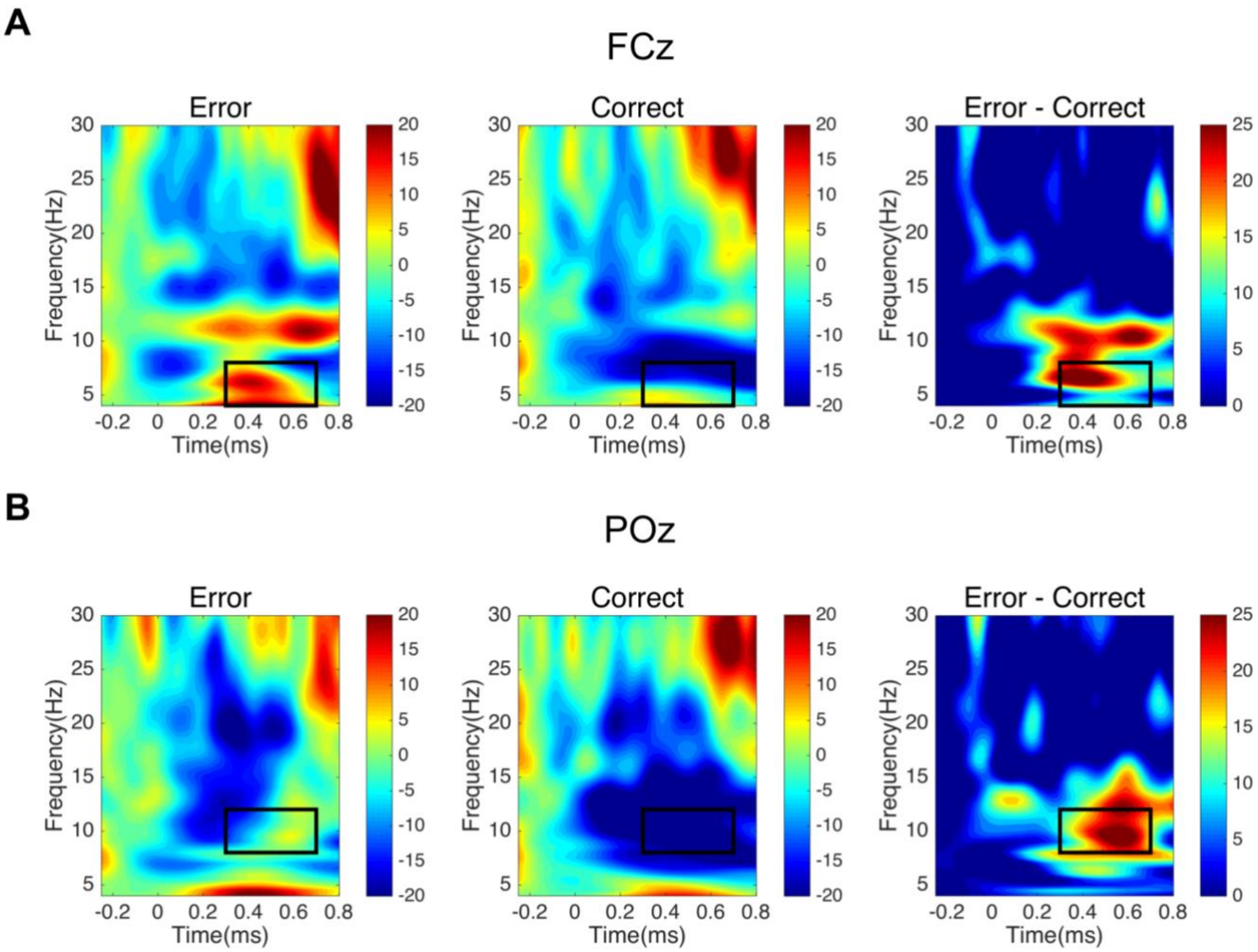


Figure 4. Time-frequency representation of Relative Power change (in %) with respect to the baseline for erroneous, correct, difference (error-correct) conditions. The onset of avatar's limb-path deviation is at 0ms; the end of avatar's action occurs at 300 ms. The black rectangles indicate the a priori chosen window of interest between 300-700ms. **A**. Erroneous, correct, difference plots at electrode FCz in the selected interval (300-700 ms) for the theta band (4-8 Hz). **B**. Erroneous, correct, difference plots at electrode POz in the selected interval (300-700 ms) for the alpha band (8-12 Hz). The black rectangles indicate the values that have been submitted to statistical analyses.

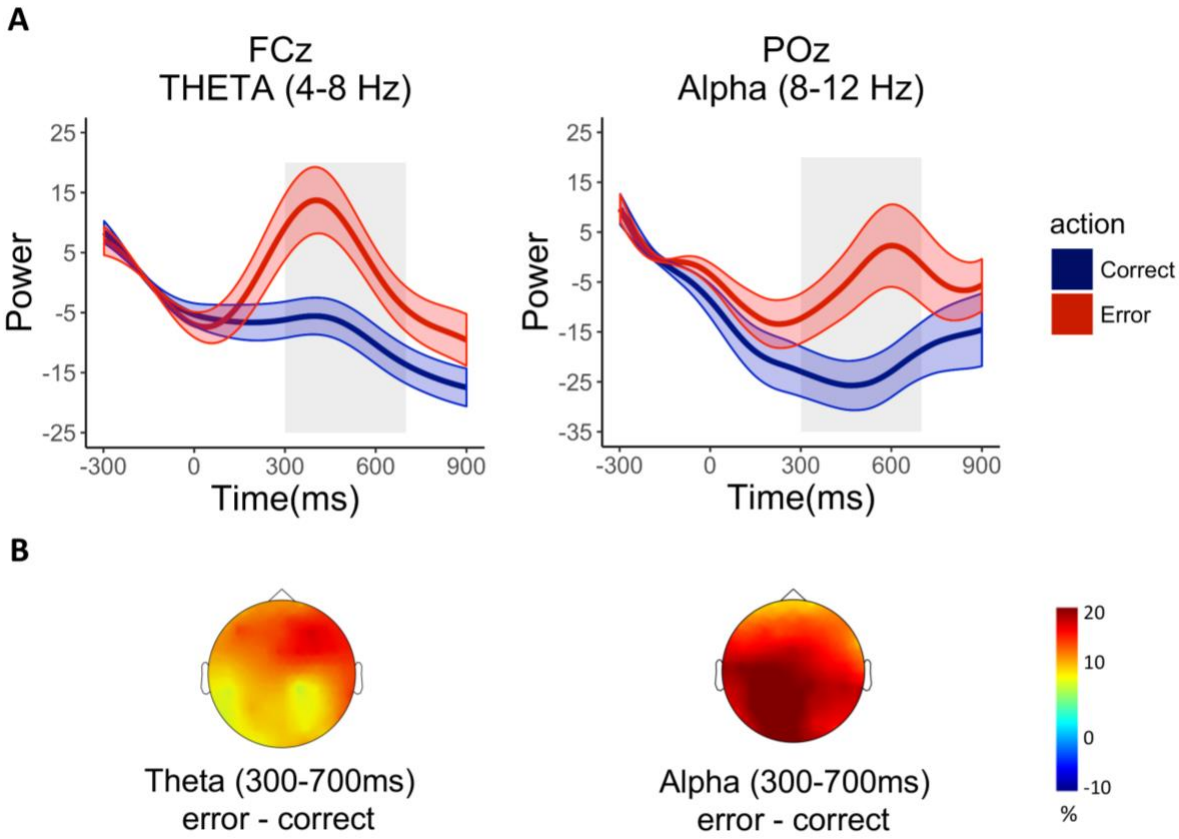


Figure 5. A. Time series representation of theta power (4-8Hz) in electrode FCz (left panel) and alpha power (8-12Hz) in electrode POz (right panel) plotted for the correct and erroneous action observation conditions. The onset of avatar's limb-path deviation is at 0ms; the end of avatar's action occurs at 300 ms. Light colors denote the standard error around the mean. Grey rectangles highlight the time window considered for statistical analysis. **B**. Topographical distribution of the ERS/D from baseline of theta (left) and alpha (right) averaged in the time window of interest (300-700 ms).

Embodiment ratings and relation with EEG signals

Preliminary application of the Shapiro-Wilk test showed that embodiment ratings were not normally distributed therefore a non-parametric analysis, including Friedman test, for within-group was used. In order to explore the link between sense of embodiment and electro-cortical indices of error processing, Spearman correlations between Embodiment ratings and error signatures (Theta and oERN) were conducted across subjects.

A significant difference in the avatar's grasp accuracy (correct vs. erroneous) in terms of sense of Ownership ($\chi^2(1)= 21$, $p<.05$) and Agency ($\chi^2(1) = 21$, $p<.05$) was found (Figure 6). As expected, there was a greater sense of Embodiment in the correct actions (Ownership: 0.59 ± 0.20; Agency: 0.48 ± 0.21) compared to erroneous actions (Ownership: 0.52 ± 0.20; Agency: 0.41 ± 0.20). The correlation analysis between theta power (range 300-700 on FCz) and Embodiment ratings revealed no significant association. Further analyses showed a negative correlation between the oERN and the sense of Embodiment. In particular, the negative correlation between the oERN and the sense of Embodiment was accounted for by the sense of Agency [r= -0.50, p= 0.02], i.e. greater negative values of the oERN were associated with stronger sense of Agency in the erroneous actions. The sense of Ownership showed a trend [r=-0.42, p=0.06] in the same direction.

Figure 6. Subjective reports of embodiment in correct and erroneous action observation conditions. On Y-axes embodiment ratings along a 1-100 points Visual Analogue Scale (VAS). Participants answered two questions: one concerning sense of Ownership ("How much did you feel the arm was yours"; 0 = no ownership to 100 = maximal ownership) and one concerning sense of Agency ("How much did you feel to control the arm" 0 = no control to 100 = maximal control). The order of the questions was randomized. The black diamond in the violin plots represents the mean value, while the grey lines connect individual subject observations between the two conditions. The rightmost panel shows a scatterplot representation of the correlation between oERN and sense of Agency.

EEG Analyses on all the incorrect trials

Analyses on the total amount of erroneous trials confirmed the results obtained with the subselection of trials. To give a holistic overview, we report main results on the time interval of interest (300–700 ms). Analyses on the theta range on FCz revealed a significant difference between the two conditions [$F(22,1)=11.41$; $p<0.005$, $\eta^2=0.34$] with greater theta power activity in the erroneous actions compared to correct ones [$M_{ERR}=5.68$; $M_{CORR}=-8.11$]. Similarly, analyses on the alpha range on FCz revealed a significant difference [$F_{(22,1)}=8.31$; $p<0.008$, $\eta^2=0.27$] with greater alpha power activity in the erroneous actions compared to correct ones [$M_{ERR}=-0.47$; $M_{CORR}=-12.93$]. significant difference for alpha range between conditions was also found on POz [$F_{(22,1)}= 11.34$; $p<0.005$, $\eta^2=0.34$]. As in the main analysis, no significant difference was found in the beta range on FCz [$F_{(22,1)}= 0.037$; $p=0.84$, $\eta^2=0$]. Analyses for the time interval during trajectory divergence (0-300ms) are also reported. In terms of theta on FCz, no significant difference was found [$F_{(22,1)}= 1.60$; $p=0.21$, $\eta^2=0.07$]. In the time domain, analyses on FCz for the oERN confirm the significant difference between conditions [$F_{(22,1)}= 8.16$; $p=0.009$, $\eta^2= 0.27$]. Analyses on Pz for the late positivity confirm no significant difference between conditions [$F_{(22,1)}=0.02$; $p=0.90$, $\eta^2=0$].

Discussion

To investigate whether the activation of the performance monitoring system is triggered by the goal violation inherently linked to erroneous events or by the surprise/novelty associated to its frequency of occurrence, we designed a study in which participants observed erroneous as well as correct actions performed by a virtual agent. The percentage of erroneous (70%) vs correct actions (30%) was opposite to what is typically used in studies with similar paradigms (Pavone et al., 2016; Spinelli et al., 2018). This manipulation allowed us to test whether the electrocortical activity associated with the observation of infrequent erroneous actions was also present when the observation of erroneous actions occurred more frequently than correct ones. We found that activity in the

performance monitoring system (as indexed by oERN and theta power; Figs. 2 and 5) was specific to observed errors despite the fact that they were the most frequent event in the series. Interestingly, posterior alpha activity was instead sensitive to the frequency of occurrence of a stimulus.

Event-Related Responses to Observed Action Error

Although ERN and Pe are typically associated to performed errors (Ullsperger, Fischer, Nigbur, & Endrass, 2014), markers of observed errors (called oERN and oPE) have been reported previously (van Schie et al., 2004; Koban & Pourtois, 2014). These studies reveal that our performance monitoring system is called into play when observing the actions of others.

A novel result of our investigation was that the oERN is not only elicited when observing an occasional slip in the action of an avatar (Pavone et al., 2016; Spinelli et al, 2018), but also when an erroneous grasp is the most frequent event in a series (Maier & Steinhauser, 2016). Furthermore, we found a negative correlation between oERN and the feeling of Agency, i.e. a greater feeling to control the virtual arm was associated with greater oERN amplitude in response to observed motor errors. These results partially mirror previous studies that found a higher feeling of embodiment associated with greater cortical response to errors (Pavone et al., 2016; Padrao et al., 2016; Spinelli et al., 2018). That being said, the relation between the sense of embodiment and brain activity is still unclear, and necessitates further investigation.

Positive parietal deflections were found for both erroneous and correct actions. This result may seem somewhat counterintuitive but merits further discussion. Positive-going error-related parietal components have been reported in previous error commission studies (Overbeek et al., 2005; Ridderinkhof et al., 2009; Koban et al., 2010). Interestingly, we found an oPe similar to the one reported in action observation studies in which erroneous trials were less frequent than correct trials (Pavone et al., 2016; Spinelli et al., 2018). In our study, the positivity found in the infrequent correct trials may represent a P300, which has been traditionally associated with task-relevant, novel and rare events (Overbeek et al., 2005). The oPe has been associated with P300 and errors (Nieuwenhuis et

al., 2001; Shalgi, Barkan, & Deouell, 2009; Koban & Pourtois, 2014). Both oPe and P300 have been further classified into an earlier frontocentral component (respectively early oPe and P3a), associated with the orientation of attention, and a later centroparietal component (respectively late oPe and P3b), associated with the conscious recognition of the event Debener et al. 2005; Overbeek et al. 2005; Ullsperger et al. 2014a).

That both erroneous and correct grasping actions elicit a parietal positive-going deflection (Figure 3) suggests that both events might be perceived as salient and meaningful (Wu & Zhou, 2009; Wessel et al., 2014): on the one hand, because it represents a violation of the default expectation of goal achievement and on the other hand, because of its rarity in the sequence. This is in line with the context-updating hypothesis (Donchin & Coles, 1988), according to which positive parietal deflection reflects the conscious and active updating of the mental model on contextual information. Similarly, this aligns with the notion that the late positivity reflects the accumulated subjective evidence collected from internal and external information (Wessel, Danielmeier, Ullsperger, 2011; Fischer & Ullsperger, 2013; Ullsperger et al., 2014). The fact that oPe was not significantly different from correct actions may also suggest that adaptation after an error, as well as post-error strategies, were not needed in our task where participants were unable to actively engage in the action. Future studies are needed to better understand the functional role of positive parietal deflections.

Cortical Oscillations of Observed Action Error

Theta and alpha modulations are considered as the oscillatory bands involved in action monitoring and error detection (Cavanagh et al., 2009; van Driel et al., 2012). Most studies have investigated cortical activity during action execution (Oliveira et al., 2007; Hajihosseini & Holroyd, 2013; Mas-herrero & Marco-pallarés, 2014). Much less is known about the modulation of these

frequency bands during action observation, as well as the impact of outcome expectancy and valence on the cortical response to observed errors.

Another novel finding of our study is that theta oscillations are not necessarily associated with rare and less expected events (Oliveira et al., 2007; Jessup, Busemeyer, & Brown, 2010) but rather with the violation of the intended goal and the significant value of an event. It is worth noting that previous studies on error monitoring show a theta response associated with errors that were always less frequent than correct actions (Tzur & Berger, 2007; Pavone et al., 2016; Padrao et al, 2016; Janssen, Poljac, Bekkering, 2016). Our data suggest that a simple motor plan - i.e. the grasp of an object on a table - is deeply encoded in our daily routine. Therefore, a violation of the plan might be a relevant and significant event that elicits a strong theta response (Figs 4 and 5).

It is also worth noting that motivationally significant errors (e.g. great monetary loss) produce enhanced theta activity (Foti, Weinberg, Bernat, & Proudfit, 2015) and larger ERN amplitude (Hajcak et al., 2005; Maier & Steinhauser, 2016) with respect to less motivationally significant errors (e.g. small monetary loss). Interestingly, this effect is found independently from the frequency of bad and good outcomes. In our case, the violation of the avatar's goal of grasping the glass – and not the money loss - can be considered the significant event that modulates the response of the performance monitoring system.

On a technical note, it has been argued that ERN and theta could reflect different ways of displaying the same result. Specifically, authors claimed that the theta response associated with errors could be the consequence of the mathematical transformation performed on the ERN during time-frequency analysis (Luu et al., 2004; Trujillo & Allen, 2007). However, it is possible to partially exclude this explanation by removing the phase-locked activity – namely the ERP activity (including the ERN) – from the signal before computing the time-frequency analysis (Sauseng, Klimesh, Gruber, Hanslmayr, Freunberger, Doppelmayr, 2007; Moreau, Pavone, Aglioti, Candidi, 2017). We applied this procedure and found differences between error trials and correct trials, with increasing theta power in the first compared to the latter condition. This result rules out that ERN and theta are merely

a different representation of the same process. Interestingly, theta power increase after the erroneous actions was greater than the effect elicited by the same actions in the time domain (note that differences concerning oERN were found but with a smaller effect size). This might be explained by the different sensitivity of time and time-frequency analyses in detecting non-phase locked activity. We believe that time-frequency analyses, that could capture both phase and non-phase locked activity, are particularly indicated to analyze the reactivity to the observation of continuous actions.

We found a parieto-occipital alpha power increase in the correct (rare) but not erroneous (frequent) actions. Although Pavone and colleagues (2016) found an opposite result of higher alpha desynchronization in the erroneous (rare) but not correct (frequent) actions, our result coalign with the idea that alpha desynchronization reflects the degree to which task-relevant events, like in our case natural grasping movements, recruit attentional resources (Klimesch, 2012). A similar result was found in an experiment by Wang and colleagues (2016) during which participants observed correct responses made by others in a speed-response task where correct responses rarely occurred. Taken together the data seem to confirm the role of alpha frequency band in the general orienting response to stimuli and re-orientation of attention (van Driel et al., 2012; Clayton, Yeung, Kadosh, 2015). The alpha synchronization we found on the frontal electrodes when observing erroneous actions merits future discussion. Although we do not have a clear explanation for this result, we speculate that the alpha increase may be related to particular error types (Van Driel et al., 2012; Pavone et al., 2016), to a transient disengagement from the task during the intertrial interval (Carp, J., & Compton, 2009), or to active internal processing of information (Sauseng, Klimesch, Doppelmayr, Pecherstorfer, Freunberger, Hanslmayr, 2005; Sausend & Klimesch, 2004; Benedek, Schickel, Jauk, Fink, Neubauer, 2014).

Overall, the EEG results found in this study cannot rule out the possibility that similar modulations can be obtained with a traditional setup (i.e. observation of movies). While only a direct 3D vs. 2D comparison may offer a straightforward response, several considerations merit further discussion. Firstly, the virtual body was previously calibrated and adapted to the participants body

size within our immersive virtual reality set-up. This created the illusion of owning the virtual body. Thus, our participants not only observed the virtual action from a first-person perspective but they also observed a real-size moving body located in the very same spatial position of the participant. Our previous studies demonstrate that: i) virtual first-person perspective is sufficient to embody the avatar without external boosting (e.g. visuo-tactile stimulation like in the case of virtual hand illusion; Tieri et al., 2015a); ii) experiencing a higher sense of embodiment elicited greater theta power in response to errors; Pavone et al., 2016). Moreover, studies that directly compared brain activity in 2D vs. 3D scenarios found that the 3D scenario required a general allocation of greater resources for cognitive control, in comparison to 2D presentations (Slobounov, Ray, Johnson, Slobounov, Newell, 2015; Vecchiato et al., 2015). Finally, all the events in our experimental paradigm occurred in a 3D real-size peripersonal space, an environment which may produce an enriched source of affordance towards the object (Costantini et al., 2007; Costantini et al., 2011; Pezzulo & Cisek, 2016) and thus maximize the salience of action errors.

Conclusions

By combining EEG and immersive virtual reality, we have been able to demonstrate that increased ERN amplitude and theta oscillatory power are associated with first-person observation of an error in the action of a virtual agent even when the error occurrence is highly probable and thus less unexpected. Therefore, our data suggest that, given its relevance (Maier & Steinhauser, 2016) an observed error (as a mismatch between the intended goal and the actual outcome) - and not its frequency of occurrence - triggers the activity of the performance monitoring system. Contrarily, we found that alpha power decrease was associated with the infrequency of a stimulus, independent of the outcome. Our results represent an important step towards understanding the involvement of middle-frontal and parietal regions during the observation of familiar erroneous and correct motor actions.

Supplementary Material of Chapter 3

Source reconstruction

Cortical EEG source imaging was performed on both erroneous and correct epochs on all 23 participants. To estimate the spatial distribution of the electrical activity in the time-frequency domain, we fitted a distributed source model consisting of 15.002 elementary current dipoles. These dipole sources were distributed at each vertex of a tessellated cortical mesh template surface derived from the standard 1 mm resolution brain (Colin27) of the Montreal Neurological Institute as provided in Brainstorm (a free open source for MEG/EEG analysis, https://neuroimage.usc.edu/brainstorm/; Tadel et al. 2011). First the head model for source imaging was implemented according to the OpenMEEG boundary element method (BEM; Gramfort et al., 2010). Based on this head model, the inverse problem was solved using sLORETA algorithm. sLORETA is a standardized variant of LORETA method, that has been shown to be robust to noise in recorded data and head model approximations with fair spatial resolution (Pascual-Marqui, 2002). The estimated dipole orientations were constrained to cortex. Noise covariance for source reconstruction was obtained separately for each subject from a baseline window ranging from -500 to -300ms, calculated on all trials. A common imaging kernel was computed and applied to obtain the cortical reconstructions on Time-Frequency data, on a trial-by-trial basis. The source reconstruction has been performed only on the Theta range of interest (4-8Hz).

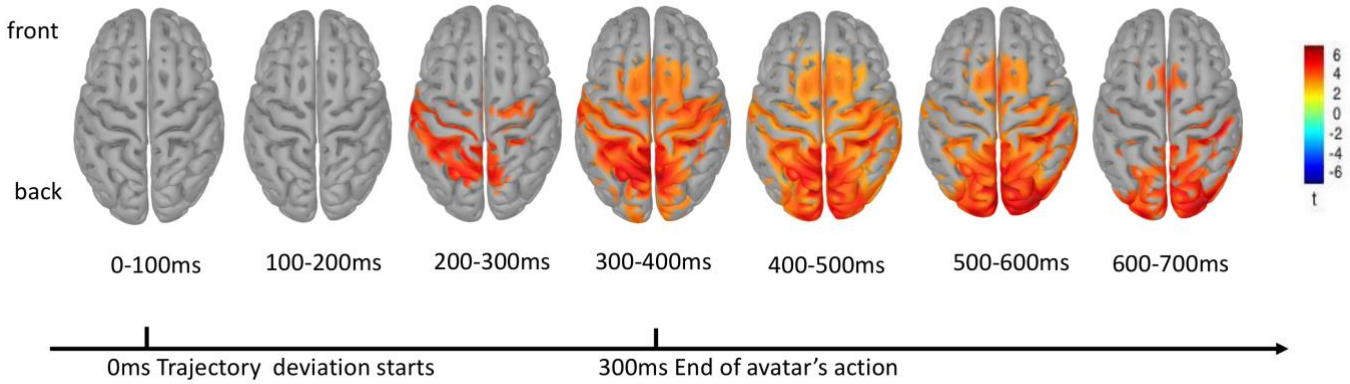


Figure 1. Source reconstruction of brain activity in the theta frequency range (4-8Hz). The figure represents t-test paired comparison ($p < 0.01$) corrected with FDR correction, in error vs. correct actions. 0 ms corresponds to the avatar's arm deviation in the erroneous action; in both erroneous and correct actions the movement ends at 300ms.

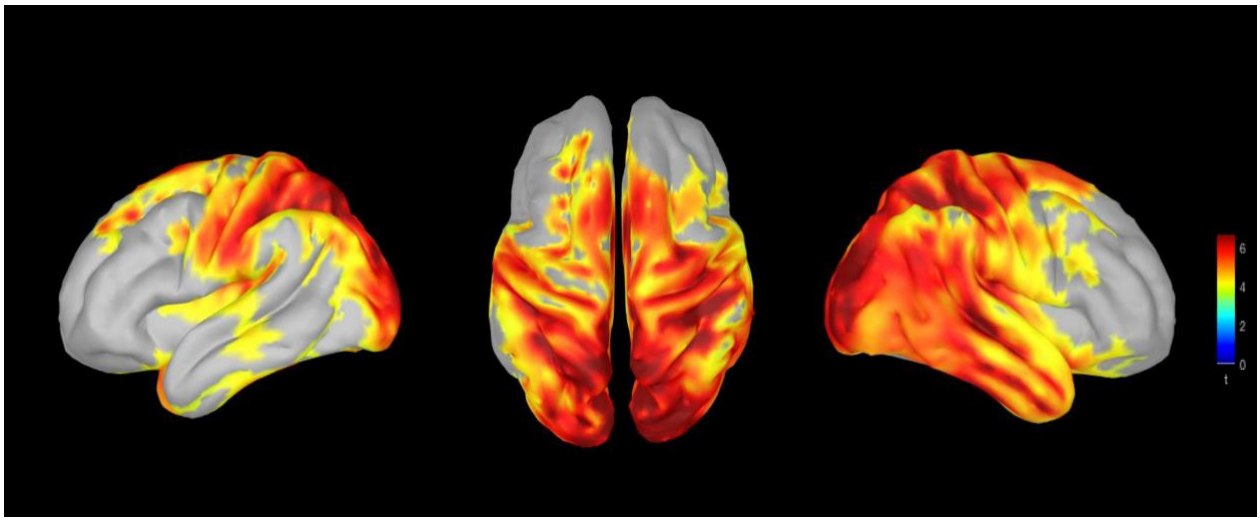


Figure 2. Cluster-based permutation on Theta (4-8Hz) at the source level in the averaged window of interest (300-700ms). The cluster-based applied uses the Monte-Carlo method of correction for multiple comparison.

Brief discussion of the source reconstruction results

Results of Figure 1 of the Supplementary Material show the t-test comparisons of erroneous versus correct actions. The t-test has been performed on several 100ms-wide windows, ranging from the beginning of the trajectory deviation (0 ms) to the end of the interval of interest (700 ms). This has been done to investigate the flow of theta activity through time, during and after the observation of an erroneous motor action. Since the analyses in the paper have been mainly performed in the interval of interest 300-700ms, also a cluster-based permutation has been done on the theta activity in this averaged time (Figure 2). The observed activity in both Figure 1 and Figure 2 suggests a prominent role of the central regions of the brain, the supplementary motor area and a wide engagement of the posterior regions of the brain. We can observe that at the end of the avatar's action in Figure 1, so at about 300ms, the theta power increased in the central regions and became prominent also in the posterior ones, were it lasted for several milliseconds. This is not of surprise considering that the error that the participants are observing is not only a goal-error, but it is a motor violation; post-error adaptation might also occur compared to correct actions, but this cannot be proved by the current study.

These results, despite interesting, still have to be taken with caution, due to the well-known limitation of the source reconstruction procedures on only 64 channels EEG-systems.

Chapter 4 Altered EEG dynamics of action and error monitoring in Ideomotor Apraxia

'From the errors of others, a wise man corrects his own'
(Publilius Syrus, 1st century BC)

Abstract

Ideomotor Apraxia (IA) refers to a high-order motor disorder characterized by the inability to reproduce transitive actions upon commands or after observation. Studies demonstrate that action observation activates the same brain networks as action execution, and provides an onlooker's motor system with appropriate cognitive, motor and sensory-motor cues to flexibly implementing action-sequences and gestures. Tellingly, the temporal dynamics of action monitoring have never been explored in people suffering from IA. To fill this gap, we studied the electro-cortical signatures of error observation in individuals suffering from acquired left-brain lesions with (A+) and without (A-) IA, and from an age-and-gender-matched group of healthy controls (H). EEG was acquired while participants observed correct and incorrect reach-to-grasps a glass in immersive virtual reality. Typical EEG signatures of error observation in time (early error positivity) and time-frequency domain (theta band-power) were not found in A+. Moreover, linear regression analysis revealed that the severity of IA (TULIA scores) was predicted by mid-frontal error-related theta oscillations, suggesting a link between error monitoring capacity and the apraxic phenotype. These results provide novel evidence of altered neurophysiological dynamics of action monitoring in individuals with IA and shed lights on the neuro-cognitive changes occurring in this disorder.

Introduction

Ideomotor Apraxia (IA) is a disorder of higher order motor control commonly associated with damage of left fronto-parietal brain networks (Buxbaum et al., 2014). IA is characterized by a complex ensemble of perceptual (Halsband et al., 2001), motor (Canzano et al., 2014; Candidi et al., 2017) and cognitive (Rothi et al., 1985; Pazzaglia et al., 2008) deficits whose interaction ultimately affects the implementation of transitive and intransitive movements upon verbal command or after

observation. According to the 'affordance competition hypothesis' (Cisek, 2007), the deficiency characterizing IA relies on an impaired selection of an appropriate action when competition between multiple actions is present. Competition arises by mere sensory exposition to an object and its physical properties that automatically triggers conflicting action schema to 'afford' the object itself (Cisek, 2007) and may lead to performance errors if the conflict is not resolved (Cooper, 2007). Tellingly, apraxic patients not only display deficits in action execution but also in action understanding and simulation (Cubelli et al., 2000; Rothi et al., 1985), in mental action imagery task (Sirigu et al., 1999), in generating internal models for action execution (Buxbaum et al., 2005), and in the judgment of the correctness of observed actions (Pazzaglia et al., 2008). Noteworthy, Pazzaglia et al. (2008) showed that deficits in action monitoring were positively correlated with difficulties in action execution, thus corroborating the thesis of a direct matching between action perception and action execution.

Action understanding is crucial for action execution. Studies suggest that humans are able to improve both their motor skills (Cross et al., 2008) and decisions on future behaviors (Ernst and Steinhauser, 2017) by observing actions from other individuals. An essential prerequisite for action understanding is the evaluation of the correctness of an observed action. EEG studies demonstrate that action errors observation underlies specific neural markers over the mid-frontal cortex, namely: the observer error-related negativity (oERN), the observer error Positivity (oPe) (van Schie et al., 2004; de Brujin et al., 2007), and increased oscillations in the theta band (4-8 Hz; Cavanagh et al., 2009; 2010; 2012). These patterns of electro-cortical brain activity are likely associated to conflict processing and resolution (Botvinick, 2001, Yeung et al., 2004; Cohen 2014; Cavanagh and Frank, 2014). Conflict arises when a unique (correct) action should be selected among a set of competing (incorrect) actions, and serves as an alarm signal conveyed from the mid-frontal to the lateral pre-frontal and posterior brain areas (Cohen and Cavanagh, 2011; van Driel et al., 2012; Cohen and Donner, 2013) to increase cognitive control over actions.

This study aims at investigating the temporal dynamics of action monitoring in patients suffering from IA by linking the 'affordance competition theory' and the 'conflict monitoring model'. Crucially, both these theories consider conflict processing as a fundamental mechanism by which the performance monitoring system exercises motor and cognitive control over actions. In view of the affordance-competition hypothesis we predict that patients with IA tend to experience high load of conflict during goal-directed action monitoring which arises from the competition between correct and incorrect action schemas. This may lead to an exaggerated burden of unresolved conflict that impairs the operation of the action monitoring system. Capitalizing on the evidence of our previous reports (Spinelli et al., 2018; Pavone et al., 2016), here we run an error observation task in immersive virtual reality in left-brain damaged individuals with and without ideomotor apraxia, and in a matched control group. Acquiring EEG signatures of performance monitoring during the observation of correct and incorrect actions will inform upon the integrity of the error monitoring system in IA, and fill the existent gap of knowledge in literature. Moreover, this evidence may shed new lights on the complex neurocognitive scaffolding characterizing IA and bring new insights of clinical interest.

Methods

Participants

Twelve right-handed, brain damaged patients were recruited from the Neuro-Rehabilitation Unit of the IRCCS Santa Lucia (Rome), following informed consent for participation. They had suffered from vascular lesions within the 24 months before the recruitment. Based on a neuropsychological assessment (see Table 1) of their symptoms, they were divided in two groups: i) patients with (A+; n= 6) and ii) without (A-; n= 6) Ideomotor Apraxia[3]. The two groups were matched for age (mean age ± SD: A+ = 63.1 ± 14.4 years, A- = 58.5 ± 14.2 years). An age-and-gender matched

[3] As it is not easy to calculate power for cluster based permutation (CBP) we calculated the power for t-test (on which CBP is based). The analysis with an estimated effect size of 1.3 indicated that our sample had 70% power for detecting significant effects on each t-tests in the CBP.

(mean age ± SD: 62.4 ± 11.2) sample of 10 healthy participants (H) was also tested. The study was conducted in accordance with the guidelines of Declaration of Helsinki and approved by the local Ethics Committees.

In order to ascertain patients' cognitive profile, standard tests and batteries for general neuropsychological assessment were administered (for details, see Table 1), including: general cognitive abilities (Raven, Court, & Raven, 1988), Verbal and Visual Memory (Spinnler & Tognoni, 1987), executive functions (non-verbal subtests of the Frontal Assessment Battery - Appollonio et al., 2005) and spatial attention (Line Bisection; Wilson, Cockburn, & Halligan, 1987). Verbal comprehension and denomination subtests of the Aachener Aphasia Test (Luzzatti, Willmes, & De Bleser, 1996) were used to assess language deficits. A multi-comprehensive assessment of apraxia symptoms was carried out by means of i) the Upper and Lower Face Apraxia test (Bizzozero et al., 2000), ii) the test for Upper Limb Ideomotor Apraxia (TULIA; Vanbellingen et al., 2010), and iii) the Ideational apraxia test (De Renzi and Lucchelli, 1988).

Subjects	Age (years)	Education (years)	Lesion	Interval from lesion (days)	Raven (10 min)	TULIA	Word Comprehension	Sentence Comprehension	FAB tot 3-6	Line Bisection
A-1	70	13	lT-F	563	32.5	222	30	28	3	9
A-2	41	18	lFP	531	30	228	28	30	2,7	9
A-3	63	13	lFpar-FI	627	29.5	231	30	24	3	9
A-4	39	13	lFP	619	27	228	29	26	3	8
A-5	51	13	lIC	688	32	234	30	30	3	9
A-6	80	13	lP	1095	26	228	30	22	3	9
A+1	70	8	lFT	473	16.5	127	20	25	2	9
A+2	80	13	lT-F	532	16.5	137	28	19	1	7
A+3	68	17	lFPI	498	31.5	180	27	13	2	8
A+4	33	13	BG	648	31.5	165	26	26	3	9
A+5	78	8	lFI	292	24.5	162	23	17	2	8
A+6	68	13	lFT	1039	24.5	192	30	25	2	9
p-value	0.38	0.29		0.44	0.09	<0.001*	<0.05*	<0.05*	<0.01*	0.21

Table 1. Demographic and clinical data reported according to the presence of IA. Asterisks indicate significance between groups (Mann-Whitney U test). Abbreviations: l=LEFT; F=Frontal; P=Parietal; par=Parasagittal; IC=internal Capsule; I= insular; T= temporal; BG= Basal ganglia.

Neural correlates of ideomotor apraxia

Although the number of participants was relatively small, we carried out an explorative analysis of the lesions in the left hemisphere damaged patients. The structural MRI/CT scans of patients were mapped with the MRIcron software (https://www.nitrc.org/projects/mricron) (Rorden & Brett, 2000) by drawing on the standard T1-weighted MRI template (ICBM152) of the Montreal Neurological Institute (MNI) coordinate system, approximately oriented to match the Talairach space (Talairach & Tournoux, 1988). For this procedure, the standard template (size: 181x 217x181 mm, voxel resolution: 1 mm^2) was rotated on the three planes in order to match each patient's MRI/CT scan orientation as closely as possible. Successively, two experienced clinicians (who were blind to each scan's group classification) traced each lesion manually on the axial slices of the rotated template, while another expert clinician checked all the drawings in a double-blind procedure. For each patient the outcome was a map of the damaged areas with each voxel labelled as 0 (intact) or 1 (lesioned). Finally, all the lesion maps were rotated back to the canonical orientation in order to align them to the standard stereotaxic MNI space (in 2mm x 2mm x 2mm voxel) and they were filtered with a custom mask based on the ICBM152 template to exclude the voxels of lesions outside the white and grey matter brain tissues.

Each patient's lesion was superimposed onto T1 templates to calculate the number of lesioned voxels in various cerebral areas and the center of the mass in each damaged area. This was then overlapped onto the Automatic Anatomical Labelling (AAL) template (Tzourio-Mazoyer et al., 2002) to provide information on the grey matter and onto the JHU white-matter atlas (Dr. Susumu Mori, Laboratory of Brain Anatomical MRI, Johns Hopkins University) for the white matter. A+ and A- lesion overlap and lesion subtraction were performed to highlight the lesioned pattern of patients' profile. Only voxels lesioned in at least 3 patients are reported.

The results (Figure S2 for details, Supplementary Material) indicate that in our sample the two groups seem to differentiate for lesions involving the Frontal Cortex, the Insula and the Basal Ganglia. Moreover, in the white matter, the involvement of the Inferior Fronto-Occipital Fasciculus and the

Superior longitudinal fasciculus supports the possibility of fronto-temporal and fronto-parietal disconnections (Catani & Thiebaut de Schotten, 2012).

1.1. Apparatus and virtual environment

Participants were seated in a four screens (3 x 3 x 2.5 m) CAVE system (Cruz-Neira et al., 1993; Figure 1 panel A). 3D images were alternatively eye-by-eye displayed at a refresh rate of 60 Hz by Nvidia Stereo Glasses, which were in turn interfaced with an Intersense 900 ultrasonic system (Thales Visionix; 6 degrees of freedom). The virtual scenario included a virtual room (3 x 3 x 2 m) with a virtual table and an avatar with both its right (R) and left upper-limb on the table (Figure 1 panel B). Atop the table was a yellow support with the virtual glass placed on it. The virtual scenario and the avatar were drawn on a 1:1 scale by Maya 2011 and 3ds Max 2011 (Autodesk, Inc) respectively, and rendered by XVR 2.1 (Huang et al., 2013; Tecchia et al., 2010). The avatar's kinematics were implemented using Halca libraries (Gillies and Spanlang, 2010). Marker events were sent to the EEG by means of a custom-made circuit governed by a digital input/output device (PoKeys 55; PoLabs; https://www.poscope.com).

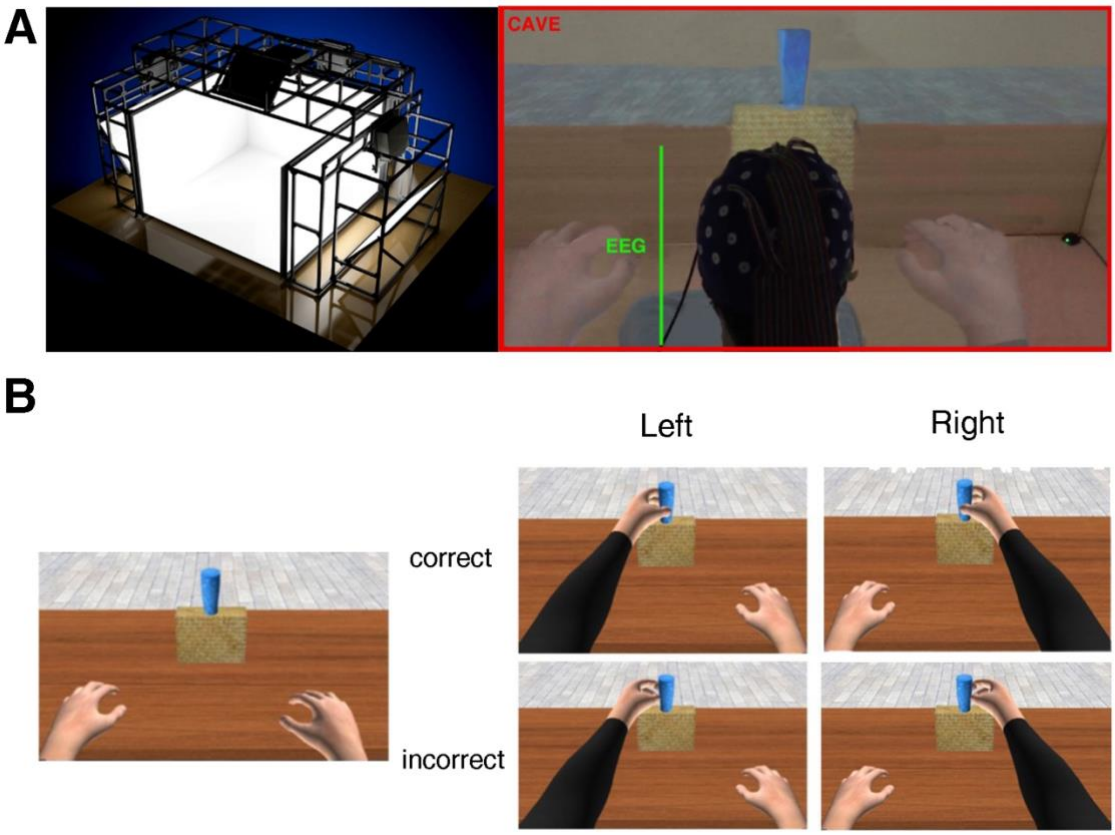


Figure 1 – Panel A: a four-screens CAVE system (left) and a snap-shot of an actual experimental trial (left) depicting a participant immersed in the virtual body in first person perspective during the EEG recording. Panel B: render of the virtual scenario as seen from the 1PP. The avatar has its own upper-limbs placed on the table at ~50 cm from the virtual glass (left). On the right-side, combinations of avatar's action outcomes that participants observed in the four experimental conditions (ACCURACY [Correct, Incorrect] * LIMB [Right, Left]).

1.2. Procedure

The task consisted in the first-person perspective (1PP) observation of an avatar's reach-to-grasp a glass errors, as in our previous reports (Spinelli et al., 2017; Pavone et al., 2016). Participants were immersed in the virtual scenario and in the virtual body in 1PP. Their own real body was occluded by a black cloth. Each trial started with an Inter Trial Interval (ITI) lasting 1250 ms (± 250 ms) in which both avatar's upper-limbs rested on the table. After a synthesized voice instructed the avatar to grasp the glass (2000 ms), participants observed one of the two avatar's limbs (R or L, depending

on the experimental block) reaching and grasping the virtual glass (Figure 1 panel B). Each reach-to-grasp action lasted 1000 ms, such that the first 700 ms were identical for all actions, and the last 300 ms defined a correct (C) or incorrect (I) outcome. While correct actions resulted in a grasping, incorrect ones consisted in a right/left-ward missing of 5 (virtual) cm from the glass. Two-thousand milliseconds (2000 ms) elapsed after the completion of each action, before the virtual limb returned to its starting position. To avoid patients' tiredness - we needed to reduce the time of the experiment. The whole experiment counted 120 trials, split in two blocks of 60 trials, each containing R or L avatar's actions exclusively. The order of blocks (R and L) was counter-balanced within participants for each group (A+, A- and H). Correct (n= 36) and Incorrect (n= 24) actions were randomly presented across the trial-list of each block. Subjective ratings of virtual embodiment (i.e., sense of ownership and vicarious agency) were collected in the 25% of trials (i.e., 30 trials).

1.3. EEG recording and analysis

EEG data were acquired by means of tin electrodes embedded in a fabric cup (Electro-Cap International, Inc), according to the 10-10 system, from 60 scalp sites (Spinelli et al., 2018). The electrode on the right earlobe served as online reference, while the ground electrode was placed on AFz. A bipolar electro-oculogram was recorded from two electrodes placed on the lateral end of the bicanthal plane. The signal was recorded by a Neuroscan SynAmpsRT (Compumedics, ltd) at 1000 Hz, and filtered with a hardware band-pass of 0.05-200 Hz. All impedances were kept below 5 KΩ. EEG traces were processed using the FieldTrip toolbox (Oostenveld et al., 2011; release: 20170607) in Matlab R2016a (The MathWorks, Inc).

For each subject, continuous EEG signals were filtered offline with a 0.5 Hz high-pass FIR filter (onepass-zerophase) and locked to the onset of the avatar's arm-path deviation (i.e., 300 ms before action-offset). This time-point corresponded to the latest time-frame in which observed grasping trajectories were still identical between correct and incorrect actions (Spinelli et al., 2018). Epochs of

6 s (± 3 s around this trigger) were extracted and sorted according to the ACCURACY of the observed avatar's action (2 levels: correct [C] and incorrect [I]), and to the avatar's LIMB that was observed (2 levels: right [R] and left [L]). Blinks and oculomotor artifacts were removed by the Independent Components Analysis. On average, 3.6 components (range: 1-7) referring to blink/oculomotor artifacts were discarded. Trials exhibiting residual artifacts were discarded by means of i) a summary plot of 3 metrics (variance, z-score, kurtosis) of all channels, as implemented in FieldTrip, and ii) a further visual inspection of all segments and all channels. Details of remaining trials are shown in Table 2. The obtained artifact-free time series were then re-referenced to the common-average reference and baseline corrected with respect to a time window of 200 ms prior to the trigger (i.e., the onset of avatar's arm-path deviation). Time- (ERPs), time-frequency (TF) domain and phase connectivity analyses (in Supplementary Material) were carried out.

	Right		Left	
	correct	incorrect	correct	incorrect
A+ **(mean; range)**	33.0; 32-34	23.0; 22-24	34.3; 33-36	23.3; 20-26
A- (mean; range)	35.0; 33-36	23.6; 22-24	34.9; 33-36	23.5; 22-24
H **(mean; range)**	34.0; 28-38	22.8; 18-27	34.0; 28-38	22.7; 18-27

Table 2 – Trial count after artifact-rejection. Results are shown for each group (A+, A-, H) and condition (Right/Left * Correct/Incorrect).

For ERP analysis, the average across trials for each condition (LIMB [R, L] * ACCURACY [C, I]) was obtained in the time-range of -200 to 800 ms. This time-window was considered for statistical analyses.

TF analysis was carried out by means of the wavelets method. Width (or cycles) of each wavelet was 4 (i.e., $4/2\pi f$). Frequency resolution was 1 Hz (range: 4-30 Hz). Length of the time window for computation was 2.6 s (± 1.3 s around the trigger). TF spectra were corrected to the relative signal change (% change) of the event period (from 0 to 1000 ms) with respect to the baseline (from -200 to 0). The average across trails for each condition was calculated in the time-window from -200 to 1000. This time-window was used for statistical analyses.

In order to estimate statistically time- and time-frequency differences between groups (A+ vs. A- vs. H) and within conditions (LIMB and ACCURACY) at each electrode, a Monte Carlo permutation was carried out, including 1000 repetitions per run. At first, a permutation distribution of the significance probabilities for dependent-samples t-tests between R vs. L was calculated for each group, separately. Since no significant results were obtained (all $p > .05$), voltage/power values of both conditions (R and L) were averaged. On these obtained time-series, dependent-samples t-tests were carried out to estimate the differences between C vs. I for each group separately. Contrasts between groups were computed by means of three independent-samples t-tests (H vs. A+, H vs. A-, A- vs. A+) using voltage/power values difference between incorrect and correct conditions (I minus C). To correct for multiple comparisons, a cluster-based correction was applied (cluster-alpha = .05) to all tests, as implemented in FieldTrip (Maris and Oostenveld, 2007).

Finally, the relation between indices of limb apraxia and brain markers of error monitoring was investigated by means of a liner regression model (i.e., $Y_i = \beta_0 + \beta_1 X_{i+} \varepsilon_i$) predicting error-related band power changes from TULIA scores (normalized in z-scores). In keeping with the time-frequency analyses, power spectra in R and L condition were averaged, and the difference between incorrect minus correct condition was obtained. From these obtained values, beta (i.e., β_1) coefficients and their p-values were calculated for each electrode and each time (from 500 to 1000 ms) - frequency (from 4 to 30 Hz) point across the A+ and A- sample, separately. The focus of this analysis was restricted

on frontal theta-band power change in the post-stimulus interval (i.e., after the onset of the arm-path deviation) as identified by the results of the time-frequency analysis.

Results

Time-domain analysis

Permutation tests resulting from the contrast between incorrect vs. correct conditions revealed significant positive clusters only for H (Figure 2 panel A). In particular, a significant voltage increase was found in incorrect trials in the 430 to 550 ms time-window, at a mid-frontal (t-max: 2.74, $p < .001$, electrode FCz; Figure 2 panel B) and occipital (t-max: 3.27, $p < .001$, electrode Oz) cluster. No negative cluster was found from this analysis. The independent-samples t-tests carried out between groups (A+ vs. A- vs. H; Figure 2 panel C) revealed positive clusters only for the contrast between H and A+. In this, H exhibited increased voltage in the time window from 420 to 560 ms at mid-frontal (t-max: 2.36, $p < .001$; electrode FC3) and parieto-occipital (t-max: 3.01, $p < .001$, electrode Oz) clusters.

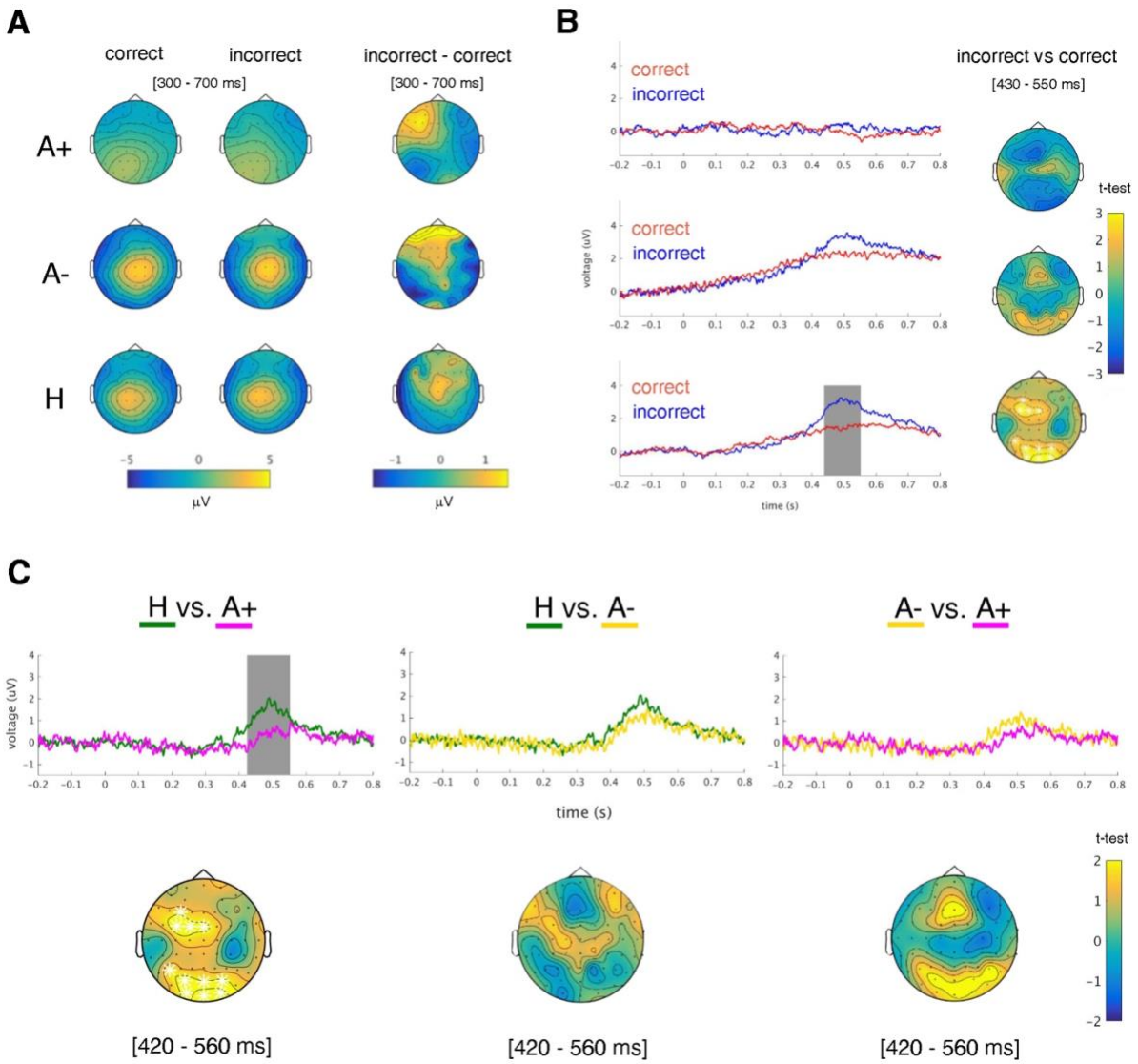


Figure 2 – Panel A: topographical maps of the oPe in the time range from 300 to 700 ms, for each group (A+, A- and H) and each condition (correct and incorrect), and for the difference incorrect minus correct condition. Panel B: time-course of oPe for each group (A+, A- and H) in correct (red) and incorrect (blue) condition at the significant fronto-central cluster of electrodes (i.e., FC1, FCz, FC2, C1). The gray-box highlights significant time-points in which oPe voltage differs between incorrect vs. correct condition. Right-ward topographical maps show the significant fronto-central cluster (white markers) resulting from the contrast between incorrect minus correct condition, for each group (A+, A- and H) in the time-range from 430 to 550 ms. Panel C: time-course of oPe (upper-row) for each group (A+, A- and H) at the mid-frontal cluster. The gray-box highlights significant time-points in which oPe voltage differs between groups (H vs A+, H vs. A- and A- vs A+). Lower-row shows significant mid-frontal and parieto-occipital clusters (white markers)

resulting from the contrast between groups (H vs A+, H vs. A- and A- vs A+) in the time range from 420 to 560 ms.

Time-frequency domain analysis

As for ERPs, the contrast between incorrect vs. correct conditions revealed significant clusters only for H. More specifically, a significant increase of theta-band (4-8 Hz) was found in incorrect trials in the time range running from 300 to 650 ms at a mid-frontal cluster (t-max: 4.78, $p < .001$, electrode FCz; Figure 3 panel A). The independent-samples t-tests between groups (A+ vs. A- vs. H; Figure 3 panel B) revealed positive clusters only for the contrast H vs A+, accounted for by the fact that H exhibited increased theta power in the time range 420-575 ms at mid-frontal (t-max: 2.39, $p < .001$; electrode FC1) and parieto-occipital (t-max: 2.74, $p < .001$, electrode CP1) clusters.

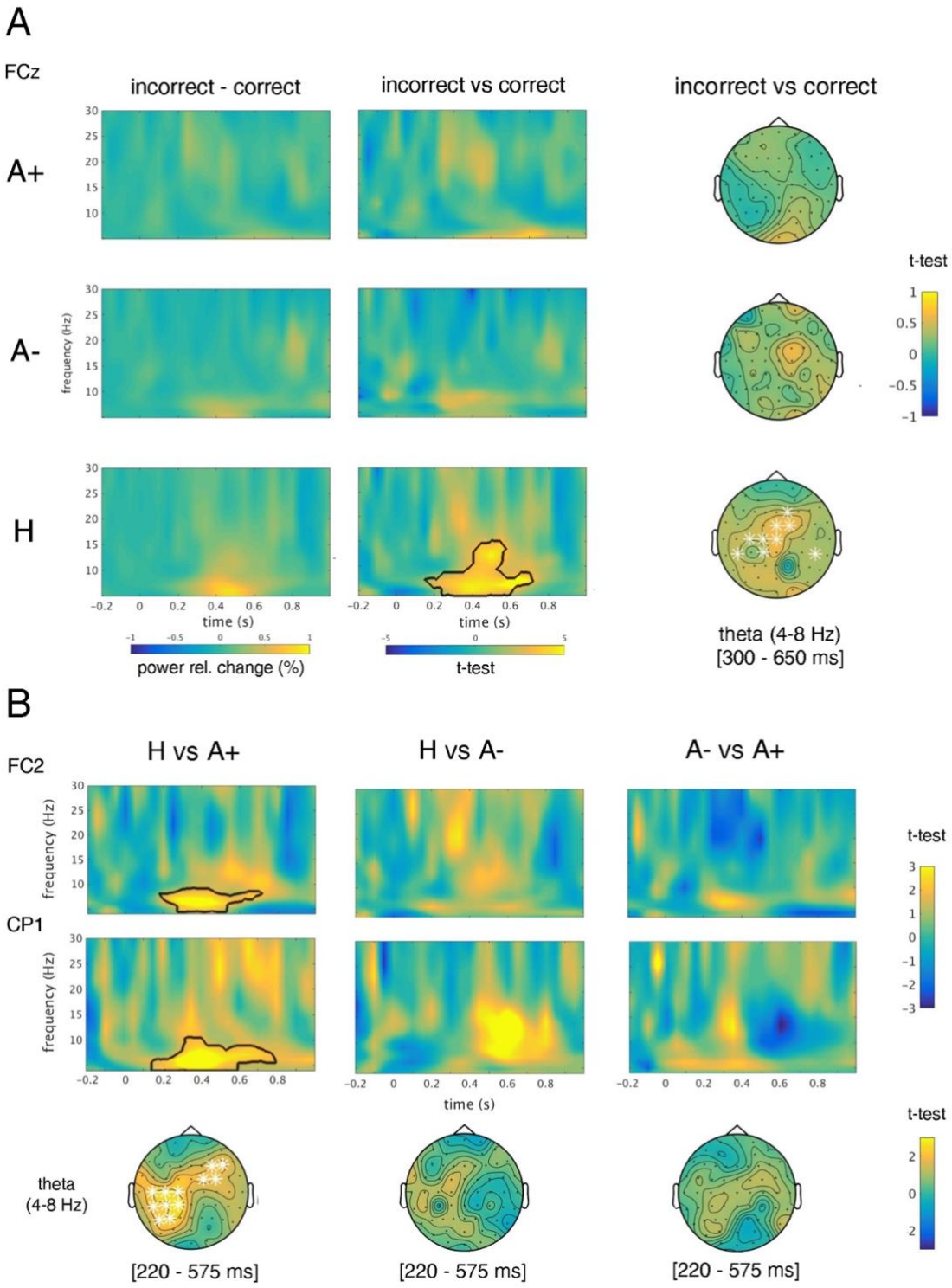


Figure 3 – Panel A: theta band-power differences (black contour-line) resulting from the contrast between incorrect and correct condition for each group (A+, A- and H) along the whole frequency spectrum (from 4 to 30 Hz). Right-ward topographical maps depict cluster of electrodes (white markers) in which theta band-power oscillations differ between incorrect vs correct condition (time-window from 300 to 650 ms). Panel B: upper-row shows statistical differences of theta band-power oscillations resulting from the contrast between groups (H vs A+, H vs. A- and A- vs A+). Lower-row depicts significant clusters of electrodes in which theta band-power oscillations (4-8 Hz) differ between groups (white markers).

Embodiment

The ANOVA resulted in a significant main effect of the ACCURACY ($F_{1,19} = 7.6$, $p < 0.02$, $\eta^2 = 0.28$), explained by overall higher values of Embodiment for Correct (mean ± SD = 0.61 ± 0.25) with respect to Incorrect (mean ± SD = 0.56 ± 0.25) action observation. This finding confirms previous evidences upon the effect of 1PP observation on the onlookers' sense of Embodiment (Spinelli et al., 2017; Pavone et al., 2016; Padrao et al., 2016). No further significant main effect nor interaction was found. Tellingly, subjective scores of embodiment did not correlate with error-related EEG signals (oPE, theta).

Predictive estimates of TULIA scores on frontal theta power

The linear regression model revealed significant results only for A+ ($F = 9.67$, $p < .05$, $r^2 = .70$, $r^2_{adjusted} = .63$). More specifically, we found a significant inverse relation ($\beta = - .27$, $p < .03$) between theta band power and TULIA scores at Fz and FC1 electrode in the time-range from 200 to 400 ms (Figure 4). No significant effect was found for A- ($F = .93$, $p = .39$, $r^2 = .18$, $r^2_{adjusted} = -.01$) in the same time-window at that electrode site.

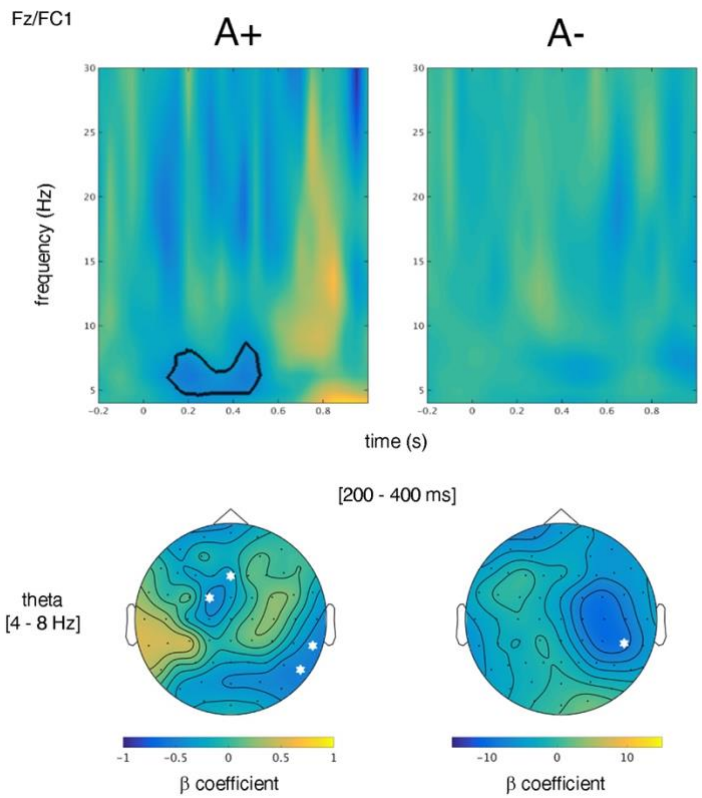


Figure 4 - Linear regression between TULIA scores and power spectra. Upper-row shows beta coefficients in the time-frequency space at Fz/FC1 for both A+ (left) and A- (right). Black contour-line highlights the time-window and the frequencies in which the effect is significant. Lower-row depicts the scalp-distribution of beta coefficients for theta band (4-8 Hz) in the time-range from 200 to 400 ms. Electrodes at which the effect was significant are highlighted in white.

Discussion

In the present study, we investigated the temporal dynamics of action errors observation in left brain-damaged apraxic (A+) and non-apraxic (A-) patients, and in a control group of healthy individuals (H). Participants' EEG was acquired during the observation of correct and incorrect reach-to-grasps presented through immersive virtual reality. Results in the time domain revealed that observation of erroneous actions brought about a suppression of early oPe in A+. Time-frequency representation of EEG data showed that error-related mid-frontal theta power was drastically decreased in A+. All in all, we provide the first neurophysiological evidence of altered performance

monitoring in patients with IA. In view of the conflict monitoring theories (Yeung et al., 2004; Botvinick, 2001) and of the 'affordance competition hypothesis' (Cisek, 2007), we hypothesize that this impairment could be driven by their original difficulty to select appropriate action schema to implement goal-directed behaviors and to suppress inappropriate conflicting affordances arising from the observation of an object. Consequently, such exaggerated burden of unresolved conflict prevents fluid action understanding and impairs EEG dynamics of performance monitoring.

Analysis in the time-domain provide a first evidence to support our hypothesis, namely the absence of the early Pe in the group of A+. Early Pe is a P300-like positive-going component that differentiates from late Pe (Falkenstein et al., 2000) for maximally peaking over mid-frontal electrodes in error trials (Ullsperger et al., 2014) and for originating from mid-frontal cortical sources (Boxtel et al., 2005). Also, early Pe dissociates from the late Pe in terms of functional significance. In keeping with P300 event-related brain potential theories (Polich, 2007), early Pe seems resembling the activity of a task-related, frontal cognitive control mechanism, whereas late Pe may be linked to higher-order processes, like subsequent memory processing or affective reaction after maladaptive/infrequent stimuli. Similarly, in view of the error-monitoring theories, these two components seem to underlie different stages of cognitive control. In fact, while late Pe is associated to error awareness (Endrass et al., 2007; Ridderinkhoff et al., 2009; Steinhauser and Yeung, 2010) or confidence in error occurrence (Boldt and Yeung, 2015), the early Pe is thought to reflect early error detection and conflict processing together with the error-related negativity (ERN; Endrass et al., 2007; Ullsperger et al., 2014). In this study, we show that A+ did not show the classical early Pe following incorrect trials, thus suggesting a reduced responsivity of their performance monitoring system to resolve the conflict generated from the competition between incorrect actions outcomes and correct action schema (Yeung et al., 2004; Botvinick, 2001). Yet, studies demonstrate that P300-like waveforms are generated by phasic activity of the norepinephrine system and may underlie learning processes to improve subsequent motor accuracy (Nieuwenhuis et al., 2005; Yu and Dayan, 2005; Dayan and Yu, 2006). Therefore, absence of early Pe in IA, may not only index a defeated

conflict processing, but also an impaired ability to use conflict resolution to implement flexible behavioral adaptation in a cascade-like sequence of neurocognitive events. Another worth discussing evidence of this study is the absence of the observation error-related negativity (oERN) across all the subjects and experimental groups. Previous studies from our laboratory (Spinelli et al., 2018; Pavone et al., 2016) and from other teams (van Schie et al., 2004; Bates et al., 2005; Koban et al., 2010; de Brujn and von Rehin, 2012), reported that observation of others' action errors brings about the presence of oERN in the onlookers' brain. Here, oERN suppression can be explainable in terms of an age-dependent effect (e.g., Gehring & Knight, 2000; Nieuwenhuis et al., 2001; Mathewson et al., 2005), or in view of the novel evidence that errors can elicit error-positivity in absence of an ERN (Di Gregorio et al., 2018). While our results fit adequately with both these cited perspectives, jumping to firm conclusions is likely complicated given the original aim of this study and the characteristics of the sample. Absence of oERN was admittedly unexpected; therefore, future works ought to disentangle this important issue.

Results indicate a significant error-related suppression of mid-frontal theta power in the group of A+. Cognitive control over goal-directed behavior is a highly flexible process that integrates task-related information according to the actual context and demands (Helfrich and Knight, 2016). A large-scale network governed by the prefrontal cortex, and composed by other distant cortical and subcortical areas (Miller and Cohen, 2001), rhythmically orchestrates such integration. Electrophysiology evidence demonstrates that activity in the prefrontal cortex becomes significantly higher when deviant outcomes (Dürschmid et al., 2016) or errors (Fonken et al., 2016) are detected. EEG studies in non-human primates also demonstrate that this multiplexed computational activity is carried out in distinct frequency bands, time and brain (scalp) locations (Akam and Kullmann, 2014). In humans, noteworthy, mid-frontal theta band power increase underlies error execution (Trujillo and Allen, 2007; Hanslmayr et al., 2008; Cavanagh et al., 2009; 2012; Munneke et al., 2015) and error observation (Spinelli et al., 2018; Pavone et al., 2016), and has been convincingly associated to conflict processing and resolution (Cohen, 2014). In keeping with time-domain results, suppression

of mid-frontal theta power in A+ suggests that conflict arising from the competition between correct and incorrect action schema is not adequately resolved in the patients' performance monitoring system.

Hence, a worth addressing issue concerns the extent to which altered performance monitoring is related to the apraxic phenotype. This was tested by means of a linear regression analysis between TULIA scores and theta power oscillations at each electrode in the time-frequency space. Results show novel evidence of a negative relation between IA and error-related mid-frontal theta power in A+, thus hinting at a close link between the severity of the disease (indexed by lower TULIA scores) and performance monitoring capacity (indeed by mid-frontal theta power increase). Such inverse effect is consistent with the idea of a compensatory mechanism by which patients' cognitive control system attempts to cope with the severity of the disease and to resolve the conflict generated by action error observation. Crucially, however, it is worth noting that our data reveal that such attempt remains insufficient in A+ who still end up showing a lowest activity of their performance monitoring system as indexed by suppressed mid-frontal theta oscillations. On this regard, further investigations are needed to explore whether theta-band oscillatory entrainment over pre-frontal cortices may facilitate patients' performance monitoring. Combination of EEG with non-invasive electrical stimulation techniques (e.g., TACS, TDCS) might shed new lights on the neuro-cognitive architecture characterizing LA and contribute to refine rehabilitation protocols. It is worth mentioning, moreover, that no conclusion can be drawn on which level of action monitoring mostly correlate with the apraxic phenotype (e.g., semantic, affective, memory), thus studies are needed to carefully inform this debate.

Concluding, an issue concerning patients' sample size deserves a discussion. Indeed, A+ group counts a relatively small number of individuals (n = 6). This is mainly due to the small prevalence of the ideomotor apraxic disease among all the other forms of apraxia, and to the adoption of very restrictive inclusion criteria based on socio-demographical data, brain-injury site and individuals' compliance to our EEG protocol in virtual reality. Therefore, while on the one hand this is a limitation

of the study, on the other it prevents us from recruiting a non-homogeneous patients' sample and jumping to misleading conclusions.

Supplementary Material of Chapter 4

Lesions

Overlap map of A+ and A- patients' lesions.

Lesion overlap showed a different pattern of involvement of cortical and subcortical structures in the two groups (Figure S1). A+ group showed a large lesion overlap in at least 3 patients that encompassed inferior frontal gyrus, rolandic operculum, insula, putamen, corona radiata, the superior fronto-occipital fasciculus and the superior longitudinal fasciculus (Table S1). This lesional pattern is in line with previous descriptions of neural lesions associated with apraxic deficits (Buxbaum et al., 2007; Goldenberg et al., 2014). A- group showed less extensive lesion overlap in at least 2 patients that included mainly the supramarginal gyrus.

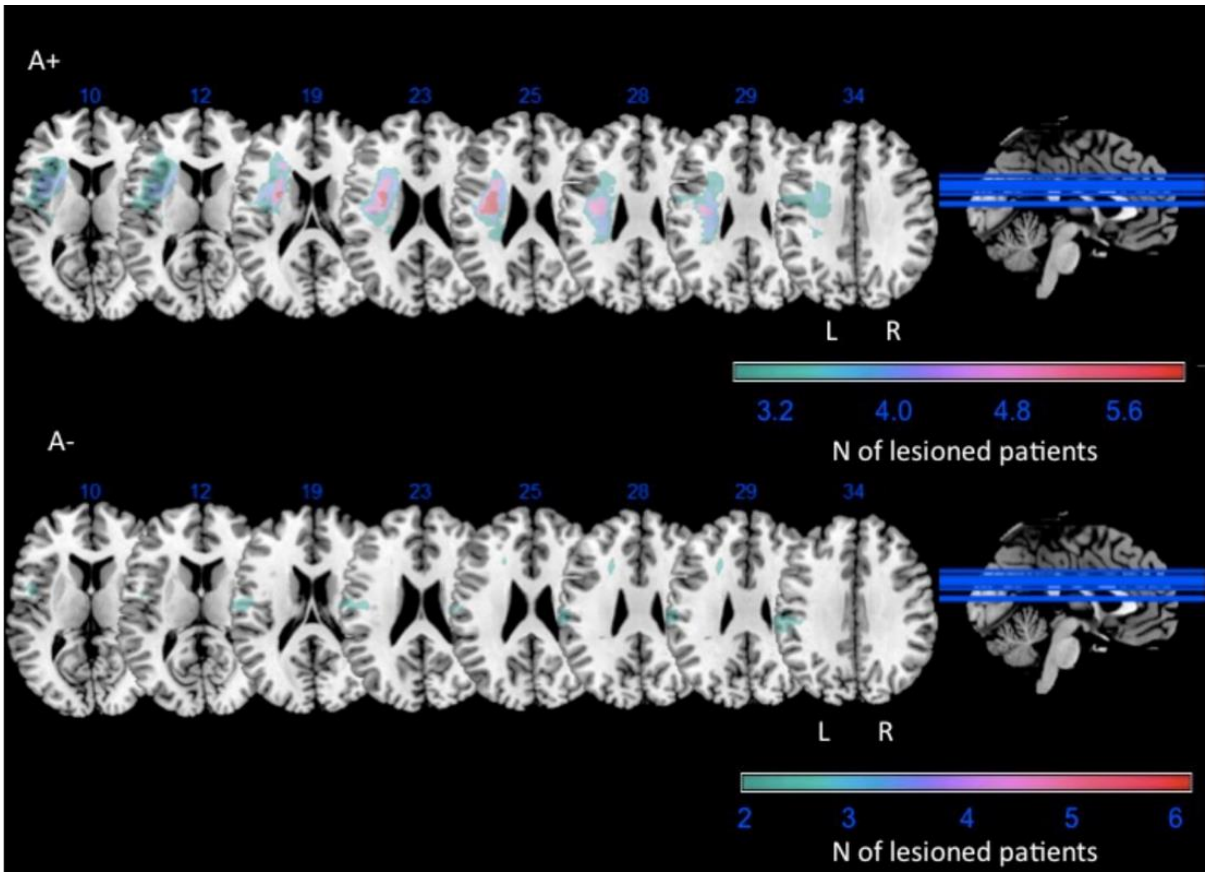


Figure S1. Lesion overlap in A+ and A-. The range of the scale in A+ goes from 3 to 6, the range of the scale in A-goes from 2 to 6 lesioned patients.

A+					
Area	Number of lesioned voxels	% of lesioned voxels	MaxX	MaxY	MaxZ
Frontal_Inf_Oper_L	1169	14	-36	5	23
Frontal_Inf_Tri_L	2048	10	-40	21	-1
Rolandic_Oper_L	3453	43	-45	-10	22
Insula_L	8349	55	-39	-9	24
Putamen_L	1348	17	-31	10	-1
Heschl_L	103	6	-47	-11	3
Anterior_limb_of_int	541	17	-26	7	17
Anterior_corona_radi	3228	47	-28	11	20
Posterior_corona_rad	750	20	-30	-31	26
Superior_corona_radi	4647	62	-29	-2	19
External_capsule_R	2146	38	-32	9	-1
Superior_longitudina	2936	44	-33	-3	21
Superior_fronto-occi	356	70	-24	4	19
A-					
Area	Number of lesioned voxels	% of lesioned voxels	MaxX	MaxY	MaxZ
Rolandic_Oper_L	452	6	-46	-1	6
Postcentral_L	2108	7	-66	-14	14
SupraMarginal_L	1710	17	-67	-26	26

Table S1. A+ and A- lesions overlap. For each region, the MNI coordinates of the center of mass along with the number (n) and percentage (%) of clustering voxels are provided.

Subtraction map between A+ and A- groups

In order to describe the regions that were most different between A+ and A- groups, the overlap of the lesions in the A- group was subtracted from the overlap of the lesions in the A+ group. Figure S2 shows the lesions that were present in at least 3 A+ patients compared to the group of A- (Table S2).

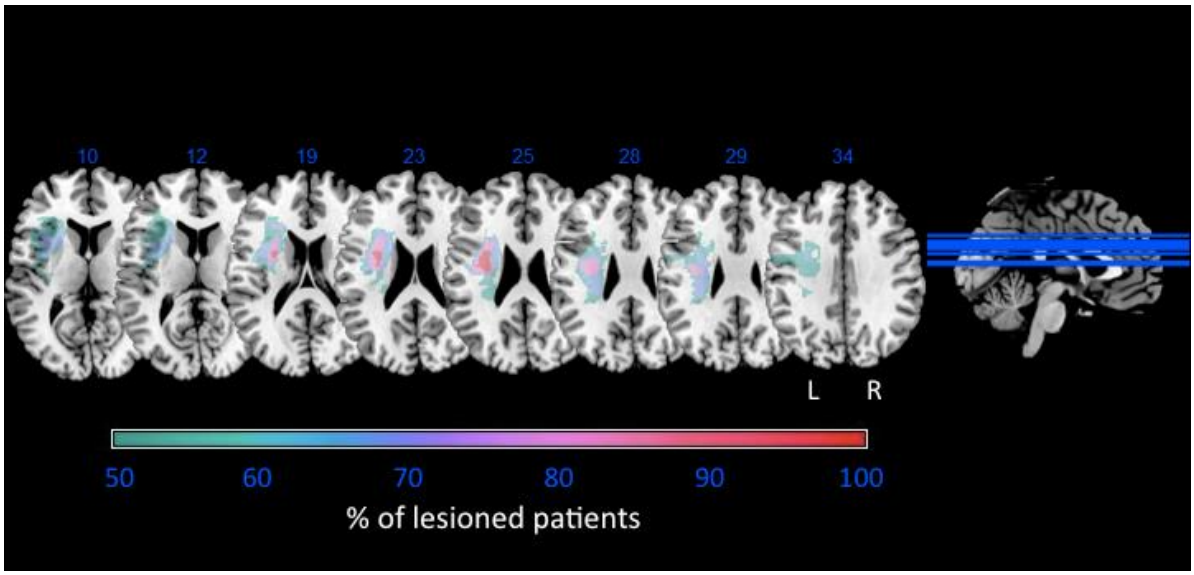


Figure S2. Subtraction of Lesion overlap between A+ and A- groups.

Subtraction 6 A+ minus 6 A- (lesioned voxels in at least 3 patients)					
Area	Number of lesioned voxels	% of lesioned voxels	MaxX	MaxY	MaxZ
Frontal_Inf_Oper_L	786	9	-36	5	23
Frontal_Inf_Tri_L	2025	10	-40	21	-1
Rolandic_Oper_L	1636	21	-42	-2	12
Insula_L	7392	49	-37	-9	24
Putamen_L	1348	17	-31	10	-1
Anterior_limb_of_int	541	17	-26	7	17
Anterior_corona_radi	2976	43	-28	11	20
Superior_corona_radi	4267	57	-29	-2	19
Posterior_corona_rad	750	20	-30	-31	26
External_capsule_R	2146	38	-32	9	-1
Superior_longitudina	2784	42	-33	-3	21
Superior_fronto-occi	351	69	-24	4	19

Table S2 Title. A+ and A- subtraction lesion map.

For each region, the MNI coordinates of the center of mass along with the number (n) and percentage (%) of clustering voxels are provided.

Lesions to inferior frontal gyrus, rolandic operculum, insula, and putamen, but also the involvement of superior fronto-occipital and superior longitudinal fasciculi seem to differentiate the two groups and are in line with A+ behavioral deficits in the prediction and error detection tasks (e.g. Kilner, 2011; Keysers and Gazzola, 2014; Avenanti, Candidi, Urgesi, 2013; Urgesi, Candidi, Avenanti, 2014). Moreover, the most significant difference between the two groups is represented by the involvement of the basal ganglia (i.e. putamen) and the insula in A+. In a meta-analysis of Yang and colleagues (2015), three networks involved in gesture comprehension were proposed. The first network involved in action observation include PMv, PMd, SPL, IPL and pSTS (Yang, Andric, Mathew, 2015). At the same time, gestures can express meanings, including concrete meanings via iconic gestures and abstract meanings via metaphoric gestures and emblems, and thus a network involved in conceptual processing is required (e.g., pMTG and IFG). Finally, gestures do not only express meaning but also convey emotions, feelings, and can have positive or negative valence, and hence a network involved in emotive processes (e.g. IFG, insula and putamen) is activated during gesture comprehension. Moreover, in literature we found that the insula, particularly anterior insula is consistently activated during errors and when performance monitoring becomes necessary (Klein et al., 2007).

Importantly, we found that superior fronto-occipital fasciculus and superior longitudinal fasciculus were also lesioned in the A+ group, thus supporting the hypothesis that deficits in our apraxic patients might have been due to the association between fronto-temporal, fronto-parietal and basal ganglia lesions.

Connectivity analysis

It is important mentioning that from a methodological point of view, connectivity results have to be interpreted cautiously due to the limitation on this kind of analyses on the electrode-level (i.e. volume conduction).

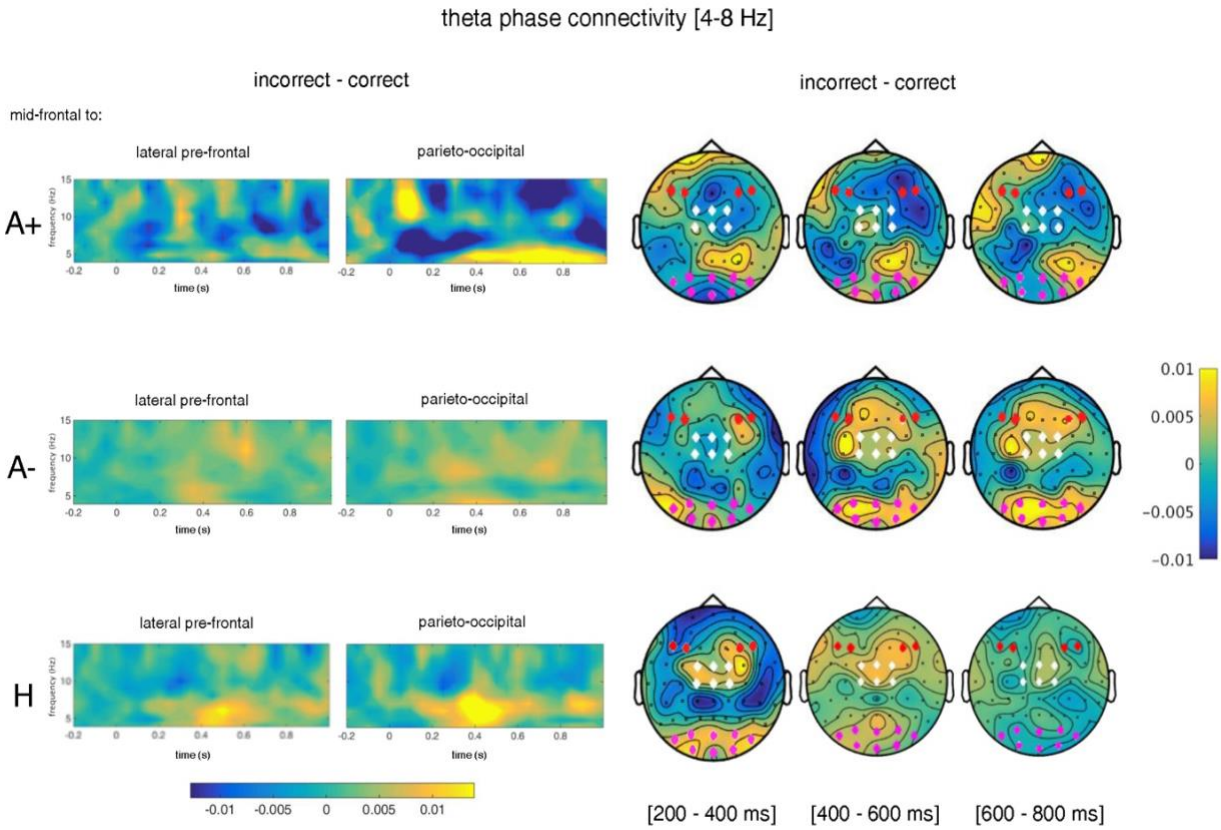
Methods

Functional connectivity analysis was carried out by computing the imagery coherence. This analysis returns only the imaginary part of the coherence spectrum and effectively suppress spurious coherence driven by electromagnetic field spread (Nolte, Bai, Wheaton, Mari, Vorbach, & Hallett, 2004). Similarly to ERPs and TF analyses, connectivity values of both condition LIMB (L and R) were averaged as no difference was found ($p > .05$). Transient theta phase oscillations from mid-frontal to lateral prefrontal and parieto-occipital brain areas have been shown to reflect a functional mechanism to increase post-error cognitive control and sensory attention (Cohen et al., 2009; Cavanagh et al., 2009; Cohen and Cavanagh, 2011) respectively. The coherence was calculated for all channel-combination and all frequencies in the time-window from -200 and 1000 ms. Then, connectivity measure between mid-frontal (electrodes FC1, FCz, FC2, C1, Cz, C2), lateral pre-frontal (electrodes F3, F5, F4, F6) and parieto-occipital (electrodes PO7, PO3, POz, PO4, PO8, O1, Oz, and O2) scalp regions were extracted for each participant in three time windows, i.e. 200-400, 400-600, and 600-800 ms. Dependent-samples t-tests were carried out to test any difference between condition (C vs. I). Differences between groups (A+ vs. A- vs. H) were estimated by means of a between-subject ANOVA, using groups (A+ vs. A- vs. H) as main factor and the differences between incorrect and correct condition (I minus C) as dependent measures.

Results

Mid- to lateral- frontal connectivity. The dependent-samples t-tests carried out between incorrect vs. correct condition revealed significant effects only for H ($t = 2.18$, $p < .016$) in the time window from 400 to 600 ms. The effect was explained by an increased theta phase connectivity for the observation of incorrect actions (Supplementary Material, Figure 1, left panel). No further significant effect was found in the other time-windows. The significant effect of the between-subjects ANOVA ($F_{2,43} = 5.43$, $p < .01$) was explained by a lower theta phase connectivity in A+ (mean: -.02, range: -.01 - .05) with respect to both A- (mean: .04, range: -.1 - .16; $p < .05$) and H (mean: .05, range: -.05 - .26; $p < .001$) in the same time-range (i.e., 400-600 ms). No further effect was found.

Mid-frontal to parieto-occipital connectivity. The dependent-samples t-tests computed between incorrect vs. correct condition revealed multiple significant effects. An increased error-related theta phase synchronization was found for both A- ($t = 2.53$, $p < .02$) and H ($t = 2.68$, $p < .01$) in the time-window from 200 to 400 ms. This effect remained significant also in the subsequent time window (i.e., 400-600) only for H ($t = 2.64$, $p < .02$). No significant effect was found in the time-window from 600 to 800 ms. The significant effect of the between-subjects ANOVA ($F_{2,43} = 3.91$, $p < .02$) was explained by a decreased theta phase connectivity in A+ (mean: -.01, range: -.01 - .03) with respect to both A- (mean: .06, range: -.12 - .15; $p < .03$) and H (mean: .04, range: -.07 - .20; $p < .05$) from 200 to 400 ms. No further significant effect was found.



Supplementary Material, Figure 1 – Theta phase connectivity between mid-frontal (FC1, FCz, FC2, C1, Cz, C2), parieto-occipital (PO7, PO3, POz, PO4, PO8, O1, Oz, O2) and lateral pre-frontal electrodes (F6, F4, F3, F5), for each group (A+, A- and H). Values refer to the difference between incorrect and correct condition and are plotted from 4 to 15 Hz for visualization purposes. Topographical maps depict theta connectivity between mid-frontal (white markers), lateral pre-frontal (red markers) and parieto-occipital electrodes (violet markers) in three time-windows (200-400, 400-600 and 600-800 ms), for each group (A+, A- and H).

Discussion of the connectivity results

Analyses of brain oscillatory activity provide another important support of altered performance monitoring in IA. It is important mentioning that from a methodological point of view, connectivity results have to be interpreted with caution due to the limitation on this kind of analyses on the scalp level (however, connectivity analyses with the imagery coherence partially limit effects due to volume conduction).

Connectivity analyses show a decreased theta synchronicity between fronto-frontal ad fronto-parieto-occipital areas in A+, with respect to both A- and H. Phase synchronicity reflects a coherent burst of activity of neuronal populations in distant cortical regions. Such alignment of brain oscillatory dynamics in time facilitates the communication between networks and ultimately enables efficient cognitive processing (Voloh et al., 2015, Daitch et al., 2013). Tellingly, fronto-frontal and frontal-parietal network dynamics has been suggested to play a crucial role for fluid cognitive control (Nàcher et al., 2013; Philips et al., 2013; Gregoriou et al., 2009). EEG studies show that post-error theta phase enhancement in these networks underlies perceptually integration of maladaptive information and represents a call to increase cognitive control for subsequent behavioral adjustment (Cohen et al., 2009; Cavanagh et al., 2009; Cohen and Cavanagh, 2011). The fact that A+ highlighted aberrant oscillatory patterns during action monitoring, suggests not only a reduced capacity of their performance monitoring system to resolve the conflict, but also a difficulty to capitalize on perceptual and sensorimotor information flow from action observation. This latter claim is in keeping with previous reports showing that motor skills of apraxic patients may influence their visual action understanding, and *vice versa* (Pazzaglia et al., 2008).

Chapter 5 Error monitoring in Parkinson's Disease: preliminary EEG data

'*Clearly*, a *better understanding of the neural networks that support action monitoring and error processing is relevant for basic psychological and neuroscience theories as well as for understanding cognitive control impairments in patient groups'. (Mike X Cohen, Neuroimage, 2011)*

Abstract

Even simple daily actions, such as grasping a glass, can become challenging in patients with Parkinson's Disease (PD). In addition to the motor execution deficits, PD patients seem to show a deficient functioning of the performance monitoring system (Farooqui et al., 2011). Previous studies on error monitoring in people with PD showed contrasting results; a few studies found the typical error-related signatures (i.e. error-related negativity, ERN; positivity error, Pe; midfrontal theta oscillations) comparable to the ones shown by healthy elderly, while others showed a general decreased cortical response to erroneous actions. In particular, the evidence on the effects of the dopaminergic medication on the brain response to errors is still unclear (Holroyd et al.,2002; Stemmer et al., 2007; Willemssen et al., 2008; Singh et al., 2018).

In the present work, by combining EEG and immersive virtual reality (CAVE system), we investigated the mechanisms underlying the performance monitoring system in PD patients during the observation of reach-to-grasp a glass actions performed by an avatar in first person perspective. The preliminary sample included 8 PD tested twice, at a 2-weeks interval. Each patient was tested in two different states namely soon after assuming dopaminergic medication ('Dopa-ON') and 12-hour after assuming the medication (overnight washout; 'Dopa-OFF'). The order of the medication state was counterbalanced across patients. Ten healthy elderly controls were also tested.

Preliminary results replicate and expand our previous findings in young participants (Pavone et al., 2016; Spinelli et al., 2017; Pezzetta et al., 2018) by showing that also healthy elderly exhibit an increased theta power activity (4-8 Hz) during the observation of erroneous actions. Interestingly, the same pattern was not found in the PD group, regardless of whether they were in Dopa -ON or -OFF state. We also found a significant difference between correct and erroneous actions in the beta range (12-30 Hz), with greater beta power in the erroneous actions, in elderly controls and Dopa-OFF participants. No such result was found in Dopa-ON participants, suggesting a link between the

dopaminergic intake and the beta response to actions. Concerning the time-domain analysis, we did not find an ERN, but all three groups showed the typical Positivity Error in response to the erroneous actions. However, in both Dopa-ON and -OFF groups the cortical potential showed lower amplitude compared to the healthy elderly.
Although preliminary, these data can help to better understand the neural dynamics of action monitoring in Parkinson's Disease.

Introduction

Parkinson's Disease is a progressive disease characterized by the degeneration of the dopaminergic neurons in the substantia nigra pars compacta, which have an impact in the fronto-striato-thalamo-circuits of the basal ganglia and the frontal areas (Chaudhuri et al., 2010). The alteration of the functionality of those circuits influence the motor abilities, which results in the typical motor features associated with the PD, namely: rest tremor, bradykinesia (i.e. extreme slowness of movements and reflexes), rigidity, abnormalities in gait and balance. Generally, the motor symptoms occur already in the early stages of the disease and often begin on one side of the body, but eventually affect both sides. Clinical and neuropsychological studies demonstrated that as the disease progresses, motor deficits are frequently associated to cognitive impairment (i.e. executive dysfunctions; Cools, 2006; Costa, Peppe, Dell'Agnello, Caltagirone, Carlesimo, 2009; Farooqui et al., 2011). The general treatment of the PD is based on the administration of dopamine at different doses to reduce the symptoms. However, it is recognized that the relation between dopamine medication and performance is individual-specific and that it follows an inverted U-shaped function, thus implying that too little and too much dopamine can impair performance (Frank, 2005; Cools and D' Esposito, 2011; Fallon, Williams-Gray, Barker, Owen, & Hampshire, 2012). Nevertheless, these are only partial results, and nowadays the consequences on the effects of the dopaminergic medication on the cognitive functioning in PD - such as performance monitoring - are not yet completely understood (Cools and D'Esposito, 2011; Seer, Lange, Georgiev, Jahanshahi, Kopp, 2016).

Few studies found the typical error-related signatures (i.e. error-related negativity, ERN; positivity error, Pe; midfrontal theta oscillations) comparable to the ones showed by healthy elderly, while others showed a general decreased cortical response to errors and conflicting events (Holroyd, Praamstra, Plat, & Coles, 2002; Verleger, Schroll, Hamker et al., 2013; Singh, Richardson, Narayanan, Cavanagh, 2018; Stemmer et al., 2007; Willemssen, Müller, Schwarz, Hohnsbein, Falkenstein, 2008; Singh et al., 2018). The evidence on the effects of the dopaminergic medication on the brain response to errors is still unclear; confounds derived from the fact that PD is a pathology characterized by heterogeneous deficits, and each patient responds to the therapy differently. Further, some studies tested the patients in both medication states, (Dopa-ON and Dopa-OFF; Stemmer et al., 2007, Willemssen et al., 2008) and some others only tested one category of patients (either patients in Dopa-ON or in Dopa-OFF; Holroyd et al., 2002). Studies that compared the patients according to their medication state showed that, in some cases, the brain response to errors was indeed modulated by the dopamine (Volpato et al., 2016), while in other cases the cortical response was unaffected by the dopaminergic treatment (Singh et al., 2018).

All the aforementioned studies on error-monitoring in Parkinson's Disease were based on speed-response choice tasks, with various degree of difficulty of the task itself (i.e. go/no go, Holroyd et al., 2002; Eriksen Flanker task, Stemmer et al., 2007; Modified Flanker task, Willemssen et al., 2008; reinforcement learning task, Volpato et al., 2016; modified Simon task, Singh et al., 2018). However, it would be relevant to understand how Parkinson's patients react to errors in very simple tasks, in which they have only to observe the correctness of actions. Also, all those studies provided only time domain analyses, but current literature suggests how extracting also time-frequency information can provide a clearer picture of the brain activity (Cohen, 2007). To date, only one study - Singh and colleagues (2018) - investigated the time-frequency response during a cognitive control task in PD patients. As already known, mid-frontal theta band activity is a crucial correlate for cognitive control (Cavanagh and Frank, 2014; Cohen, 2014b) and response to executive demands,

and it is diminished in PD during a variety of tasks such as the interval timing task, in which participants estimate an interval of several seconds as instructed by a cue. These 4-8 Hz theta rhythms are modulated by cortical dopamine and can be abnormal in patients with PD. Humans and rodents with dysfunctional dopamine showed impaired performance in a timing task and had attenuated delta and theta activity (Parker, Chen, Kingyon, Cavanagh, & Narayanan 2015). The topographic distribution of ERPs over midfrontal cortex showed a typical central distribution. However, as Parker et al. (2015) specifies, it is likely that those oscillations are not unique to the timing tasks, but are rather a cortical response elicited by alerting and orienting responses, as a need for cognitive control (Cavanagh and Frank, 2014). It is still unclear if mid-frontal theta activity is attenuated also during tasks that require error detection in PD patients. Additional work is also needed to dissect whether there are relative effects of the dopaminergic treatment in the theta response to errors (Seer et al., 2016).

In this study we used the paradigm developed in our laboratory (Pavone et al., 2016; Spinelli et al., 2017; Pezzetta et al., 2018) to investigate the error mechanisms in response to simple observed actions. The same patients visited the lab twice, in both dopaminergic treatment states (Dopa-ON and Dopa-OFF); an aged-matched group of healthy participants were also tested. The current analyses are done on a preliminary set of data.

Methods and Materials

Participants

Eight patients with Parkinson Disease (PD) took part in the experiment (3 females, 5 males; mean ± SD: Age: 72.25 ± 9.84; Years of Education: 10.13 ± 3.23). All participant had normal or corrected-to-normal visual acuity (one patient had reduced visual acuity with the left-eye). Patients that were diagnosed with idiopathic PD were included in the study (United Kingdom Parkinson's Disease Society brain bank criteria; Huges, Daniel, Kilford, & Lees, 1992). The inclusion criteria were: i) absence of dementia (Mini Mental State Examination, MMSE> 26); ii) absence of other

neurological and psychiatric diseases; iii) stable anti-Parkinsonian therapy; iv) sickness duration of less than 10 years. In addition, a group of 10 healthy control subjects (HC) was included in the study, comparable to the group of patients by age and level of education (6 females, 4 males. Mean ± SD: Age: 72.71± 8.82; Years of Education: 14.43 ± 2.53). They were included according to the following inclusion criteria: i) absence of neurological and/or psychiatric diseases in anamnesis; ii) absence of subjective cognitive disorders; iii) not taking medications with psychotropic action iv) MMSE = 30. To determine patients' cognitive profile and to exclude a diagnosis of dementia, neuropsychological batteries were administered during a first visit in the laboratory, while patients were under their dopaminergic treatment (i.e. Dopa-ON; Test results in Supplementary Material). Patients that met our criteria of inclusion were then contacted to take part to the experiment.

The PD group visited the laboratory twice, seven days apart: once in-within one hour from the medication intake (Dopa-ON) and once after a 12-hour overnight washout from their individual prescriptions of dopaminergic medication used to treat PD (Dopa-OFF). The medication sessions were counterbalanced in the experiment. One control subject was excluded from the analyses because he was not matching our inclusion criteria. A final sample of 8 PD Dopa-ON, 8 PD Dopa-OFF (within participants, each of the 8 Parkinson was tested twice) and 9 Healthy participants were included in the analyses. The present results included in this Chapter have to be considered as preliminary; the aim is to test 20 subjects per group, that given the large effect investigated (eta partial square ~0.45 for theta power) largely satisfy the requested sample size.

Apparatus, Stimuli, and Procedure

Similar to the Procedure described in the studies of Chapters 2 and 3 of the present work, participants sat in a cave automatic virtual environment (CAVE) with projectors directed to four walls of a room-sized cube (3m X 3 m X 2.5 m; Cruz-Neira et al. 1993). The virtual scenario consisted of a basic room with a table. At the center of the table, a yellow parallelepipedon was located with a blue glass on top of it. Participants observed one avatar in first-person perspective (1PP; see Fig. 1)

seated on a chair in front of a table with its arms resting on the table. The glass was placed in the avatar's peripersonal space at a distance of ~ 50 cm (Costantini et al. 2011). The avatar and the scenarios were created by means of Autodesk Maya 2011 and 3D Studio Max 2011, respectively. The kinematics of the avatar were implemented by HALCA library (Gillies and Spanlang 2010), and the experiment was performed in an immersive three-dimensional (3D) virtual environment with a real-size avatar drawn on a 1:1 scale and rendered in XVR 2.1 (Huang et al. 2013; Tecchia et al. 2014). Participants wore Nvidia stereo glasses in which 3D virtual images were alternately displayed on both eyes with a refresh rate of 60 Hz. Moreover, these stereo glasses were interfaced with an Optitrack system and constantly tracked the head position during the experiment.

Experimental Procedure

Before the beginning of the experiment, participants underwent a familiarization phase with the experimental setup, as well as a calibration phase within the virtual environment, which consisted of adapting the size of the virtual body to the real one. The participants were engaged in 3 minutes eyes-open resting state in which they were asked to be relaxed and observe the scenario in front of them, followed by 3 extra minutes of resting state after the end of the task (the analyses on these sessions are not reported in the thesis). After this phase, a brief practice session (8 trials, 4 correct and 4 erroneous) occurred. Each participant was informed that the goal of the avatar's movements was to reach and grasp the glass on the table and that the action might or might not be successful. The total number of trials per participant was 110, 70 of which were correct and 40 of which were incorrect (similarly to Pavone et al., 2016). The total duration of our experiment was approx. ~20 min. At the onset of each trial, a sound signaled the beginning of the action. During the trial, participants observed the movement of the avatar's right arm in 1PP. The total duration of the movement was of 1050 ms; the kinematics of the movement were identical for the 70% of the action in both conditions and diverged in the last 30% of the movement, leading to either a successful or unsuccessful grasp (Pavone et al., 2016; Spinelli et al. 2017). The deviation from the to-be grasped object was identical

in all the erroneous trials (Fig. 1). The sequence of correct and incorrect trials was randomized. After the end of the action, the avatar's arm rested for 1000 ms (± 50 ms) before a black screen appeared. During the intertrial interval (ITI), three different situations could occur: 1) in 10 trials (4 incorrect, 6 correct), participants had to answer a catch question ("Did the arm take the glass?" (yes/no answer); 2) in 65 trials, an empty black screen was presented; and 3) in 35 trials (12 incorrect, 23 correct), participants had to provide ratings concerning the sense of embodiment. When the first and third cases occurred, the black screen lasted until a vocal response was given, whereas when the second case occurred, the experimenter pressed a key to start the next trial, producing a variable ITI (mean duration: ~4,000 ms, range 2000-6000ms). To measure their sense of embodiment, participants were asked to verbally rate the embodiment questions on a visual analog scale (VAS) from 0 to 100. The question was about their sense of ownership ("To what extent did you feel the arm was yours?"; 0 = no ownership to 100 = maximal ownership; Slater et al. 2010; Fusaro et al., 2016; Tieri et al., 2015a, 2015b). A total of 208 embodiment ratings were collected for each group of Parkinson patient, and 315 embodiment ratings for the healthy group.

Statistical analyses were performed using R software (R Core Team 2014). ERPs and time-frequency statistical analyses were performed using the erpR package (Arcara and Petrova, 2014). As data were normally distributed, analyses were performed using repeated-measures ANOVA, and Greenhouse-Geisser correction for nonsphericity was applied when appropriate. All ANOVAs were performed using the ez package (Lawrence, 2013). Practice trials were excluded from the analyses.

EEG recording and processing

The EEG recording procedure was identical to the steps written in Chapter 2. The only difference was in the EEG caps which included two additional parietal electrodes as compared to the settings in the previous chapters. For easy of reference, we will briefly explain the EEG recording and preprocessing also here. EEG signals were recorded using a Neuroscan SynAmps RT amplifier system and 62 scalp electrodes embedded in a fabric cap (Electro-Cap International), arranged

according to the international 10–10 system1[4]. Horizontal electro-oculogram was recorded bipolarly from electrodes placed on the outer canthi of each eye. EEG signal was recorded continuously in alternating current mode with a bandpass filter (0.05–200 Hz) and sampling rates of 1.000 Hz. Impedances were kept under 5 k. All electrodes were physically referenced to an electrode placed on the right earlobe and re-referenced offline to the common average across all electrodes.

Offline, raw data were band-pass filtered with a 0.1-100 Hz filter (finite impulse response filter, transition 40–42 Hz, stopband attenuation 60 dB). Independent component analysis (ICA; Jung et al. 2000) was performed on the continuous EEG signal and components that were clearly related to blinks, ocular artifacts, sweat were removed (on average, 3.4 ICA components). For ERP analyses, an additional bandpass filter (0.3–30 Hz) was applied on the continuous raw signal. EEG signal was then downsampled to 500 Hz and epoched in wide windows of 3-s length, from -1.5 to +1.5 s to avoid edge artifacts induced by the following wavelet convolution. Epochs were time-locked (0ms) to the end of the avatar's arm-path deviation (Pavone et al., 2016). All epochs were DC offset corrected to the previous 200 ms preceding the end of the movement. Each epoch was then visually inspected for artifacts to manually remove residual eye blinks or epochs exceeding -100/+100 μV amplitude. Bad channels were not interpolated, and they were excluded from the analyses. Analyses were performed using the Brainstorm toolbox for Matlab (free open source for MEG/EEG analysis, https://neuroimage.usc.edu/brainstorm/; Tadel et al. 2011) and customized Matlab routines (Cohen 2014).

EEG analyses

For the time-domain, analyses focused on the oPe. The oPe is a P300-like component peaking at the Pz electrode likely associated with the conscious recognition of errors, either committed (Vidal et al., 2000; Pavone et al., 2009) or observed in others (de Bruijn et al., 2007). All ERPs analyses

[4] The EEG was recorded from the following channels: Fp1, Fpz, Fp2, AF3, AF4, F7, F5, F3, F1, Fz, F2, F4, F6, F8, FC5, FC3, FC1, FCz, FC2, FC4, FC6, T7, C5, C3, C1, Cz, C2, C4, C6, T8, TP7, CP5, CP3, CP1, CPz, CP2, CP4, CP6, TP8, P7, P5, P3, P1, Pz, P2, P4, P6, P8, PO1, PO2, PO7, PO3, AF7, POz, AF8, PO4, PO8, O1, Oz, O2, FT7, and FT8.

were based on mean amplitude (Luck 2005). We performed a time-point cluster-based permutation analyses with 1000 repetitions for each run ($p < 0.05$) and MonteCarlo correction in an extended time window from 0 (end of avatar's action) to 600ms. For the time-frequency analysis, we used a complex Morlet transformation to compute time-frequency decomposition. A mother wavelet with central frequency of 1 Hz and 3 s of time resolution (full width half maximum, FWHM) was designed as in Brainstorm software (Tadel et al. 2011). The other wavelets were computed from this mother wavelet and ranged from 1 to 80 Hz, with 0.5-Hz linear frequency steps. To normalize each signal and frequency bin separately with respect to a baseline, we computed the relative power change (in %) over the time-frequency decomposition as

$$F = \frac{\mathrm{S(t,f)} - \mathrm{Sbase\ (t,f)}}{\mathrm{Sbase(t,f)}} * 100$$

where S(t, f) is the signal spectrum at a certain given interval of time (t) and frequency (f), and S_{base}(t, f) represents the signal power of the reference signal used as baseline. To avoid edge effects, the power activity from -700 to -500 ms, a window in which the avatar's movement was identical in erroneous and correct conditions, was used as the baseline interval. Positive and negative values index a decrease or an increase in synchrony of the recorded neuronal population (Pfurtscheller and Lopes da Silva 1999) with respect to a given reference interval, where equal neural activity is expected between conditions. In our case, a relative power increase/decrease represents a modulation of power compared with the mean power activity during the baseline. As in Pavone et al. (2016), the main analyses were computed on FCz and Pz electrodes, focusing on oPe in the time-domain (200-600ms) and the mid-frontal theta activity in the time-frequency domain (0-600ms). For the time-frequency domain analyses, after computing the Morlet convolution on the Frequencies 1-80 Hz, we squeezed the frequency of interest on the following: delta (2-4 Hz), theta (4–8 Hz), alpha (8 –12 Hz), and beta (13–30 Hz) bands. Similarly to the ERP analyses, in the time-frequency, separately for each frequency band, we performed a time-point cluster-based permutation analyses with 1000 repetitions

for each run ($p < 0.05$) and Montecarlo correction from 0 (end of avatar's action) to 600ms. Both for time and time-frequency domain, with positive and negative cluster we refer to the grouping of neighboring significant effects in time, space (and frequencies) with the same sign (positive or negative).

For each group within analyses are performed. Then the differential outcome (obtained by subtracting the correct from the erroneous conditions) was compared within patients in condition Dopa-OFF and Dopa-ON, to investigate a direct effect of the dopaminergic treatment on the error monitoring. The same was done also between the PD groups (PD Dopa-ON and PD Dopa-OFF) and the healthy participants, to investigate differences between the error monitoring system in healthy and pathological populations (similarly to Singh et al., 2018). Embodiment ratings are analyzed.

Results

Cluster-based permutation

Event-related potentials – oPe

Cluster-based statistics found significant clusters differentiating erroneous compared to correct actions for the three groups, but with different extension in time. In the HC a positive cluster ($p = 0.01$) was found starting from 240 to 570 ms, with greatest spatial extent of the cluster reached at 332ms. In the PD Dopa-ON a positive cluster ($p = 0.001$) was found in the range 300 to 600 ms, with largest spatial extent at 518ms. Finally, in the PD Dopa-OFF a cluster was found ($p = 0.002$) in the range 374-600 ms and largest spatial extent at 482ms. The topographical scalp maps (Fig. 1C) show the clusters in the averaged window 0-600ms. Direct cluster-comparisons between groups did not show significant differences.

Delta (2-4Hz)

Cluster-based statistics found significant clusters for the three groups, with different extension in time. In all cases the clusters showed greater delta activity for erroneous compared to correct

actions. In the HC a positive cluster was found from about 0 to 600 ms (p = .005), and it was located over the posterior regions (Table 1 of Supplementary Material), reaching the largest spatial extent at about 318ms. Another middle-central positive cluster was found in the PD Dopa-ON (p = 0.04), from 0 to 600ms, and largest spatial extent at 600ms. A middle-central cluster was found also in the PD Dopa-OFF (p=.04) lasting from 0 to 600ms and showing a maximal activity at 352ms. No difference between groups was found at a cluster level.

Alpha (8-12 Hz)

No significant activity was found between erroneous and correct actions in the three groups.

Theta (4-8Hz)

Cluster-based statistics found a significant, positive cluster (p=.02), only for the HC, which was present from about 80 to 560 ms and was spread over the central and posterior regions, reaching the largest spatial extent at about 298ms (Figure 2C). The cluster in the HC showed greater theta activity for erroneous than for correct actions. The PD showed no significant cluster in neither PD-Dopa ON nor Dopa-OFF conditions.

A significant contrast was found between HC and PD-Dopa OFF (in which the mean values obtained by correct minus erroneous actions – respectively for each group - were compared). More specifically a comparison between independent groups found a positive cluster for HC compared to PD Dopa-OFF (p = .03) in the theta-band, from 100 to 480ms at a mid-frontal cluster, reaching the largest spatial extent at 250 ms (Figure 2C).

Beta (12-30Hz)

Cluster-based statistics found a positive cluster (p=.04), for the HC, which was present for a short window from 0 to 190 ms and was located over the central regions with a slightly contralateral distribution compared to the observed arm (Figure 2D). The PD Dopa-ON showed no significant

cluster. The PD Dopa-OFF showed a positive cluster (p = .002), with a greater activity in the erroneous than correct actions from 240 to 600 ms, with largest spatial extent at about 570ms and an activity mainly located on the central electrodes (Figure 2D).

The independent-samples t-tests between groups compared the difference value obtained by correct minus erroneous trials and was performed between these groups: HC vs. PD Dopa-ON; HC vs. PD Dopa-OFF. The analysis revealed positive clusters for the contrast HC vs PD Dopa-OFF (p=0.04), accounted for by the fact that PD Dopa-OFF exhibited increased beta power in the time range 430-600 ms at the fronto-central electrodes (Figure 2D).

Analyses on a-priori chosen electrode

In the time-domain, the oPe and its topographical distribution can be seen in Figure 1. Traditional analyses on electrode Pz showed that while the HC group reached a significant difference between erroneous and correct actions ($t(8) = -3.81$, $p = 0.005$, $M_{ERR} = 10.93$ µV; $M_{CORR} = 7.91$µV), the same was not showed by the two PD groups (PD Dopa-ON: [$t(7) = -2.26$, $p = 0.06$, $M_{ERR} = 6.14$ µV; $M_{CORR} = 3.53$ µV; PD Dopa-OFF ([$t(7) = -2.13$, $p = 0.07$, $M_{ERR} = 4.83$ µV; $M_{CORR} = 2.75$ µV). The fact that oPe is not significant at the single electrode level (Pz) but it is significant at a cluster-level, is accounted by the fact that the cluster found in the Parkinson's groups (when erroneous and correct actions were compared), showed a greater activity in the central rather than parietal electrodes. Thus, the analysis at a cluster-level might have captured more information, as a more frontal rather than parietal activity for the oPe.

In the time-frequency domain, traditional theta frequency band analyses (4-8Hz) on electrode FCz comparing erroneous versus correct actions found that in the HC there was a significant difference between action type (HC: [$t(8) = -2.60$, $p = 0.03$, $M_{ERR} = -3.54$; $M_{CORR} = -16.04$), that was not found in the PD groups (PD Dopa-ON [$t(7) = -1.00$, $p = 0.35$, $M_{ERR} = -8.20$; $M_{CORR} = -14.11$), PD Dopa-OFF [$t(7) = 0.004$, $p = 0.99$, $M_{ERR} = -22.44$; $M_{CORR} = -22.40$), thus confirming the findings on a

cluster-level. Thus theta activity for erroneous trials is significant only for the control group (HC) both at a cluster level and by analyzing the typical electrode of reference, FCz.

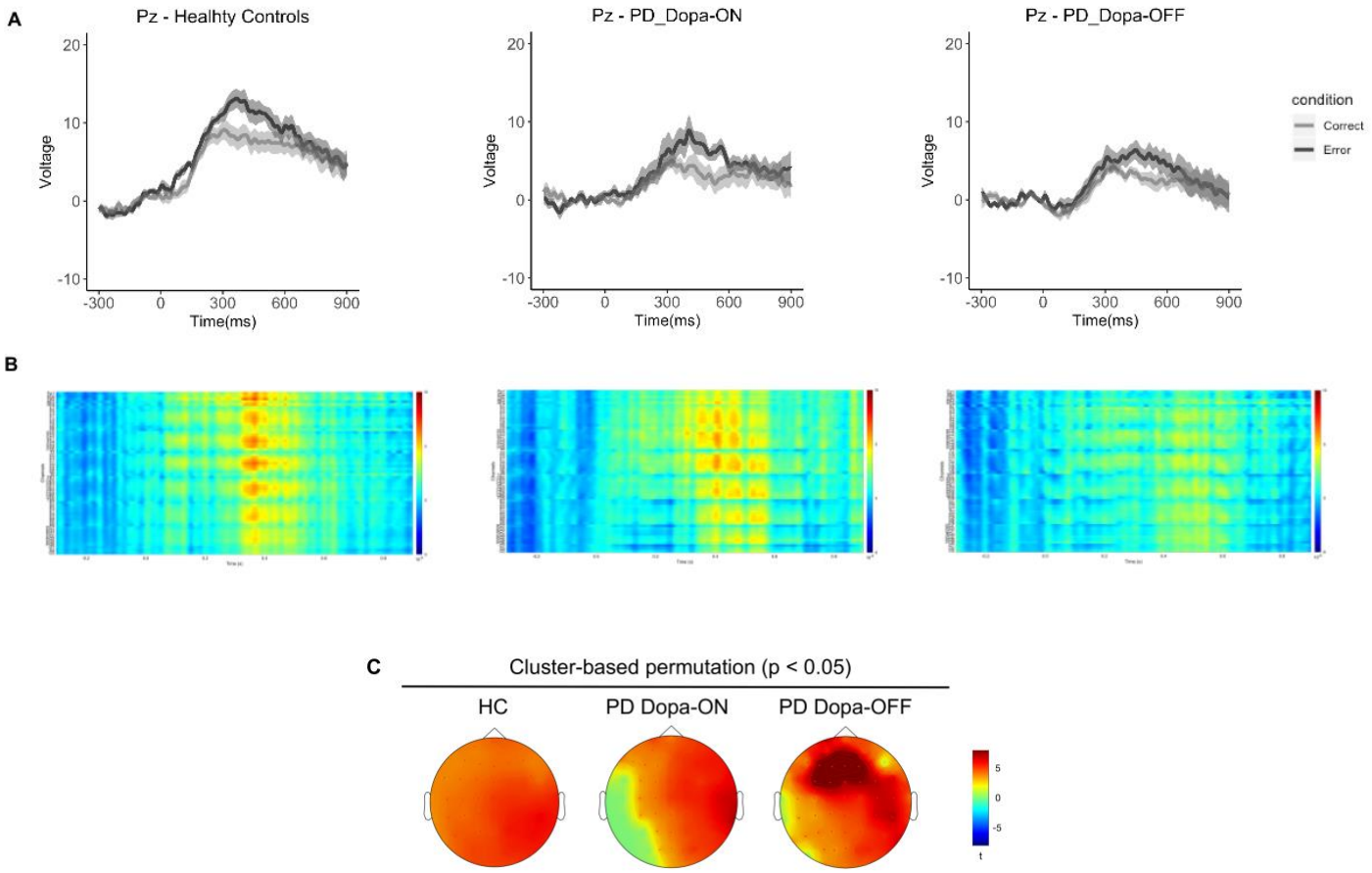


Figure 1. Electrophysiological results in the time domain for each group **A.** Grand average waveforms of oPe at electrode Pz. The end of avatar's movement is set at 0ms. Light colors denote the standard error around the mean. **B.** Graphical representation of voltage distribution across channels. The values are the result of the erroneous-minus correct action (y-axis: channels, x-axis: time in ms). **C.** Cluster-based permutation (dependent sample t-test with cluster-correction $p<0.05$) for erroneous versus correct actions in the three groups. The maps represent the time-point in which the cluster was found with largest spatial extent.

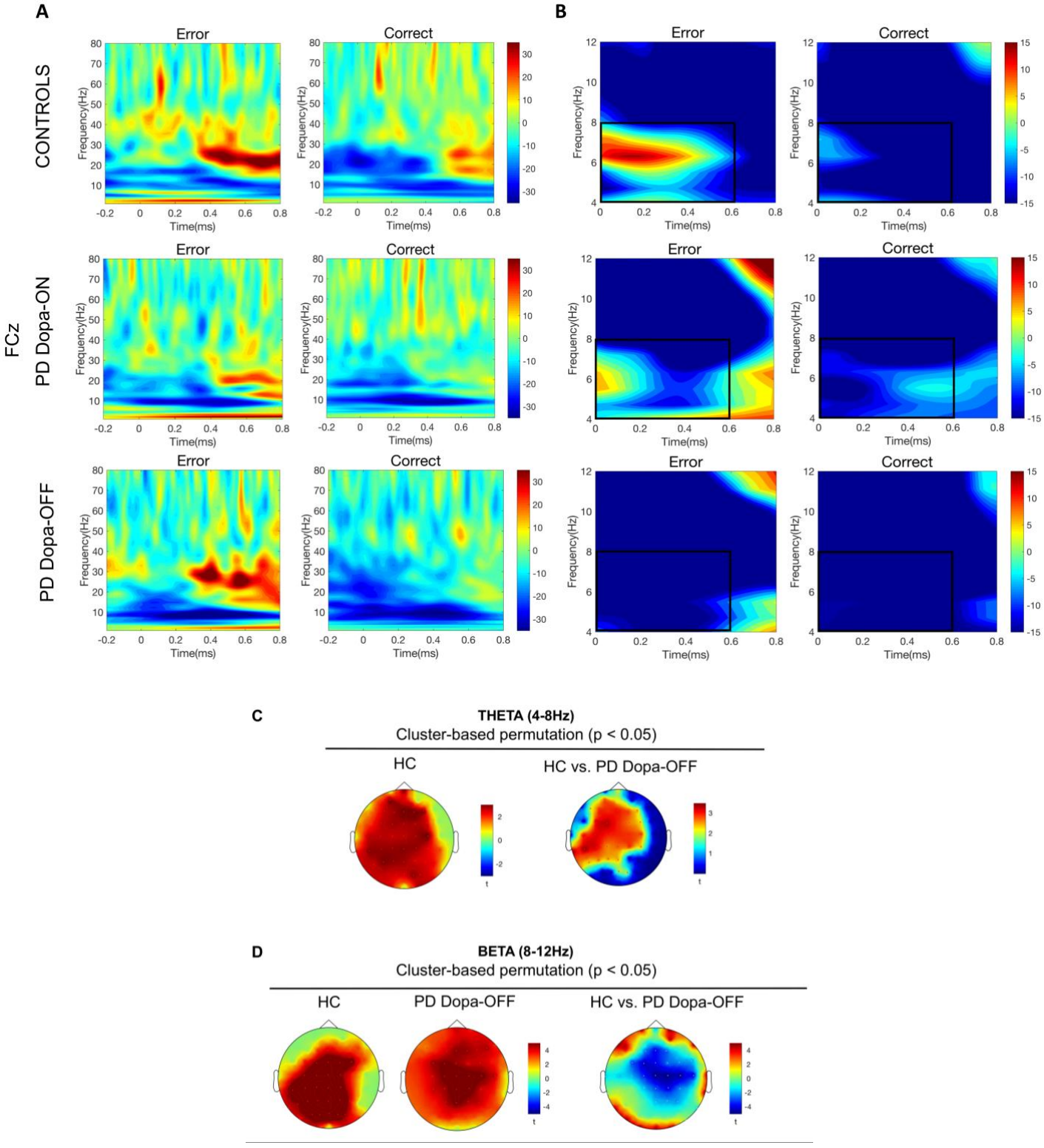


Figure 2. Time-frequency representation of Relative Power change (in %) with respect to the baseline for erroneous and correct conditions. The end of avatar's limb-path deviation is set at 0ms. **A**. Erroneous and correct plots at electrode FCz in the three groups, with all frequencies 1-80Hz displayed **B**. Erroneous and correct plots at electrode FCz in the zoomed range of interest, only frequencies from 4 to 12 Hz are displayed. The black rectangles highlight the a priori chosen window of interest between 0-600ms and 4-8 Hz, that

indicate the values that have been submitted to statistical analyses. **C.** Cluster-based permutation ($p<0.05$) for erroneous versus correct actions in theta. Only the HC showed a significant cluster. Independent Cluster comparison ($p< 0.05$) found a positive cluster only when HC and PD Dopa-OFF were compared, with the HC showing greater theta activity in the fronto-central electrodes. Only significant cluster are displayed in the figure **D.** Cluster-based permutation ($p<0.05$) for erroneous versus correct actions in beta. HC and PD-OFF showed a significant cluster. In the PD Dopa-ON no cluster was found. Independent Cluster comparison ($p< 0.05$) found a positive cluster when HC and PD Dopa-OFF were compared, with the HC showing less beta activity in the fronto-central electrodes. Only significant cluster are displayed in the figure. The maps represent the time-point in which the cluster was found with largest spatial extent.

Embodiment

Preliminary application of the Shapiro-Wilk test showed that embodiment ratings were normally distributed therefore parametric analyses for within- and between-groups were used. In order to explore the link between sense of embodiment and electro-cortical indices of error processing, Spearman correlations between Embodiment ratings and error signatures (Theta and oPe) were conducted across subjects. Paired sample t-test for each group showed no significant difference in the avatar's grasp accuracy (correct vs. erroneous) in terms of sense of Embodiment (Healthy Control: $t(8) = -0.33$, $p = 0.74$; PD-Dopa ON = $t(7) = 0.05$, $p= 0.96$; PD-Dopa OFF: $t(7) = 0.21$, $p = 0.83$). Also, in this preliminary sample, we did not find a correlation between the sense of Embodiment and neurophysiological signatures (oPe, theta).

Discussion

In the present study, we investigated the temporal dynamics of correct and erroneous action observation in Parkinson patients, in two different experimental conditions: i) once right after their dopaminergic treatment (PD Dopa-ON) and ii) once after a night of dopaminergic withdrawal (PD Dopa-OFF); a control groups of healthy individuals (HC) was also tested. Participants' EEG was acquired during the observation of correct and incorrect reach-to-grasps presented through immersive virtual reality.

Results in the time-domain revealed that observation of erroneous actions produced an oPe in all the three groups (detailed information about clusters latency in the *Results section – Cluster-based permutation Event-related potentials – oPe*), but with a different latency as revealed by cluster-analyses. Time-frequency analyses showed that error-related mid-frontal theta power was not present in PD patients, regardless of whether they were in Dopa -ON or -OFF state. Differently, the control group of HC participants showed the typical error-related theta increase that has already been observed in young healthy samples (Pavone et al., 2016; Spinelli et al., 2017; Pezzetta et al. 2018). A greater beta activity was found in PD patients only when in Dopa-OFF and not -ON condition, suggesting a relation between beta oscillations and dopamine. Compared to most of existing studies, that mainly investigated the integrity of the error-monitoring system in the time-domain, we showed how complementary and additive information is present in the frequency domain.

These preliminary data suggest that patients with dopaminergic loss have an altered monitoring system from a neurophysiological point of view, compared to healthy controls.

From visual inspection of the ERP graphs across the experimental groups, we did not observe an error-related negativity (oERN). Similarly to the Study on apraxic patients in Chapter 3, oERN suppression can be explained in terms of an age-dependent effect (e.g., Gehring & Knight, 2000; Nieuwenhuis et al., 2001), or in view of the novel evidence that errors can elicit error-positivity in absence of an ERN (Di Gregorio et al., 2018; Tan, Vandeput, Qiu, Van den Bergh, von Leupoldt, 2019). The fact that the stimuli used in this task are continuous actions rather than all-or-none events (as are usually in speed response tasks – e.g. Flanker task) might also contribute to make more difficult to observe time-locked potentials as the oERN compared to other strong deflections (e.g. oPe). All the three groups (HC, Dopa-ON and Dopa-OFF) showed a significant positive cluster in the time-domain when erroneous and correct actions were compared, which suggests that an oPe is elicited in the erroneous actions in both HC and Parkinson patients. However, the three groups showed a different topography and latency of the oPe, as revealed by the cluster's latencies.

Moreover, since extensive literature points to the parietal regions of the scalp as the ones in which the oPe can be largely seen, we also performed traditional a-priori analyses on the electrode Pz. Interestingly, when Pz was considered, only the HC group showed a significant difference, whereas the Parkinson' patients, neither in Dopa-ON nor Dopa-OFF, showed a statistically significant distinction between conditions. The different result between the traditional analyses (single electrode) and the cluster-based ones is accounted by the fact that the electrodes found in the cluster are mostly located in the central - rather than parietal – areas. This activity might be associated with the early oPe, that is the positivity related to the low-level detection of an error. The early oPe is a component that share similar features with the P3a, an event-related potential associated with the orientation of attention (Overbeek et al., 2005). The late oPe on the other side has been instead associated with the P3b and linked with the awareness of the event and the updating of the recently acquired information.

Interestingly, Luu and colleagues (2004), found that in a filtered signal, most of the energy of the Pe was not concentrated in the theta band, but rather in the slower delta band. We thus performed also the analyses on the delta frequency range (2-4Hz) and we found that the cluster-based permutation showed that all the three groups evidenced a significant cluster when erroneous and correct action were compared, but only the HC showing a parietal distribution. The results of the delta activity are thus quite in line with the ones found in the time domain (oPe) for the electrode Pz**,** which shows a significant difference between erroneous and correct trials only in the HC group. The Parkinson's groups – regardless dopaminergic treatment - show no significant difference in such a posterior electrode; however when analyses were performed at a cluster level, also the groups with Parkinson patients showed a cluster – more anterior than posterior - suggesting that both oPe (in the time-domain) and delta activity (in the time-frequency domain) might involve mostly the anterior regions of the scalp, in the Parkinson patients.

However, these analyses rely only on evidence collected at the scalp-electrode level, further analyses on the source level might shed light on the cortical areas involved in the processes, in the three groups.

As for what concerns the theta activity, only the HC group showed the typical theta increase when observing erroneous actions, whereas both PD group, in either medication conditions, did not.

Reduced theta activity was previously found in timing and novelty response tasks (Cavanagh, Kumar, Mueller, Richardson, Mueen, 2018; Chen et al., 2016; Kim et al., 2017; Parker et al., 2015). Only recently this has been extended to cognitive control (Singh et al., 2018). In this study Singh and colleagues tested 16 PD twice (Dopa-ON and Dopa-OFF) in a modified speed-response Simon task, and they found no theta activity after erroneous events in both groups, regardless dopaminergic medication. Several studies confirmed that mid-frontal theta signals are a mechanism of cognitive control, which engage the involvement of medial frontal cortex as well as other connected areas (Cohen, 2011; Cavanagh and Frank, 2014; Cavanagh and Shackman, 2015; Holroyd and Coles, 2002). Parkinson patients' accuracy in answering the questions in the catch trials ("Did the arm take the glass") revealed that PD were able to understand whether an error or a correct action occurred. In fact, patients typically made zero or one mistakes within the entire session (only one PD in Dopa-OFF committed several errors when in -OFF, but not when he was in -ON). Despite behavioral accuracy, the fact that there is a lack of theta response in the Parkinson' patients suggests that the mechanism is alternated as compared to that of the healthy aged-matched controls, even when the PD are under dopaminergic treatment. An interesting result here is the fact that Parkinson patients on one side did not show an increased theta power to the occurrence of errors, but on the other side it was still possible to observe an oPe, despite with a more central than parietal scalp distribution. This might be in line with the recent results of di Gregorio and colleagues (2016), in which that found a dissociation between the early response of the monitoring system (usually the ERN/theta) and the Pe response, suggesting a complex and hierarchical architecture of the monitoring processes.

Concerning the alpha activity, we were surprised not to find a difference between erroneous and correct actions in the three groups, especially in the healthy old participants, as was the case in

previous studies with a similar paradigm (Pavone et al., 2016; Pezzetta et al., 2018); however, the modulation of some frequencies seems particularly age-dependent; for example, Babiloni et al., (2006) suggest that the occipital delta and posterior cortical alpha rhythms decrease in magnitude during physiological aging, with both linear and nonlinear trends. The fact that other studies on healthy young participants with a similar paradigm (Pavone et al., 2016; Pezzetta et al., 2018) found a modulation in the alpha band, while experiments on aging and pathological populations did not, might follow that idea.

In addition to the absent theta response, PD Dopa-OFF showed an atypical long beta synchronization after the erroneous actions that was not present in the PD Dopa-ON patients and that was present only as a brief contralateral beta rebound in the HC. This enhanced beta activity that we found in the PD Dopa-OFF deserves further discussion. Previous evidence in literature has showed that the passive observation of a movement is characterized by beta suppression. The beta increase in synchrony – or beta rebound - that follows the end of movement is believed to reflect the active inhibition or general deactivation of the motor system (Pfurtscheller, Neuper, Brunner, & Da Silva, 2005; Jurkiewicz, Gaetz, Bostan, Cheyne, 2006). Local field recordings on the subthalamic nucleus identified excessive neural oscillations in the β-band in PD patients as well as a general increased rhythmic activity associated with pathophysiological aspects (Oswal, Brown, Litvak, 2013). Also, Engel and Fries (2010) suggested that the pathological enhancement of beta-band activity is likely to result in an abnormal persistence of the status quo and a deterioration of flexible cognitive control. However, when the dopamine depletion is compensated by the dopaminergic treatment, the beta activity might be restored to a functional activity (Doyle et al., 2005). In our study, the fact that the increased beta activity was found in the erroneous but not in the correct actions, is in line with some prior findings on healthy adults (Koelewijn et al., 2008). Koelewijn and colleagues (2008) showed beta rebound was stronger for the observation of incorrect than correct actions, suggesting a potential role of the beta activity in the evaluation of action significance. The over-response that we observe during the dopaminergic withdrawal, goes along with the findings linking the Parkinson's Disease to a

pathological beta response. Still these interpretation needs to be supported by further investigations. In particular, collecting data on additional and larger samples will help clarify the modulation of these oscillations in response to action monitoring.

In the embodiment ratings, we were surprised not to find a difference between erroneous and correct actions in the groups, as was the case in previous studies with a similar paradigm (Pavone et al., 2016); however it might be the case that aging people had a different sensitivity to explicitly refer their sense of embodiment on the observed action; also, in previous studies (Pezzetta et al., 2018), we observed that the sense of Agency correlate with the brain responses to actions. In this case, for a matter of time, since the task could not last more than 25 minutes (to be able to test the PD Dopa-ON in their maximum peak of medication), we decided to include only the sense of Ownership question. One limitation of the current study is the fact that PD were tested twice, whereas HC were seen once time. However, as also previous works (Singh et al., 2018), we can reasonably exclude a learning effect, since the task is of simple action-observation and it is not related to the acquisition of task-specific abilities. Further, it is important to underline that our sample size is considerably low as in the current sample we tested only 8 PD and 9 control participants. Thus, the results should be considered only preliminary, as should the related interpretations. An objective of the present study is in fact to reach a full sample of 20 PD Dopa-ON, 20 PD Dopa-OFF and 20 matched HC. Previous error monitoring studies on Parkinson patients had a low number of participants (generally 10-15, always < 20; Seer et al., 2016) or tested the patients only in one of the two therapeutic conditions (Dopa-ON/OFF), making difficult direct comparisons across studies. Furthermore, since the Parkinson's Disease is an heterogenous pathology, characterized by different levels of gravity and impairment, it is important to enlarge the sample in order to achieve more firm information.

Conclusions

Some of the most debilitating aspects of PD include motor and cognitive disturbances. While it is widely appreciated that cell death in PD somehow contributes to deficits in higher cognitive

functioning, the mechanisms underlying these deficits remain somehow unclear. In this investigation, we tested PD patients during dopaminergic treatment and after night withdrawal, to test the integrity of the monitoring system, by focusing on the modulation of error-related signatures. The findings reported here, despite preliminary, suggest the deficient theta may be a promising candidate correlate for studying cognitive dysfunction in Parkinson's Disease.

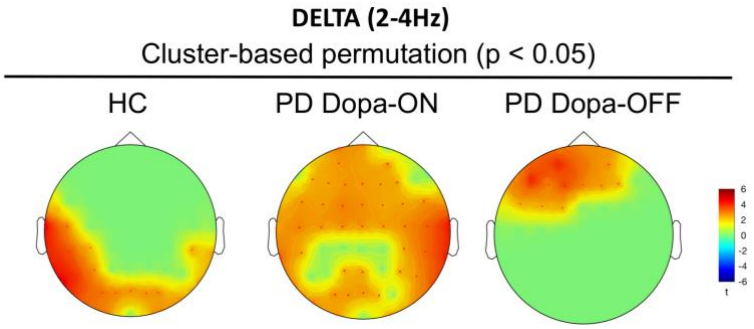


Figure 1. Cluster-based permutation (p<0.05) for erroneous versus correct actions in delta (2-4Hz). All three groups showed a significant cluster. The maps represent the time-point in which the cluster was found with largest spatial extent.

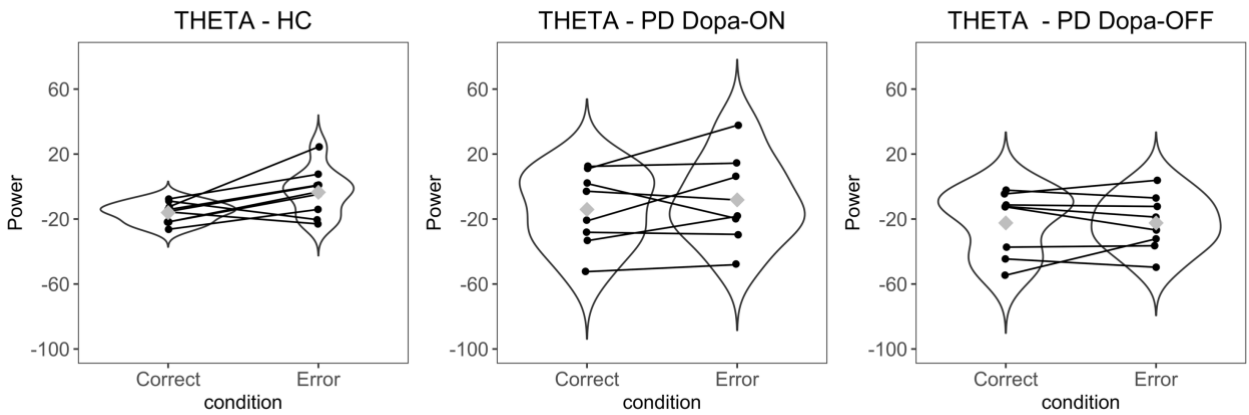


Figure 2. Single subject values of theta in the averaged window 0-600ms, in correct and erroneous conditions. On Y-axes power expressed in percentage (%), as % increase or decrease compared to the baseline period. The grey diamond in the violin plots represents the mean value, while the black lines connect individual subject observations between the two conditions.

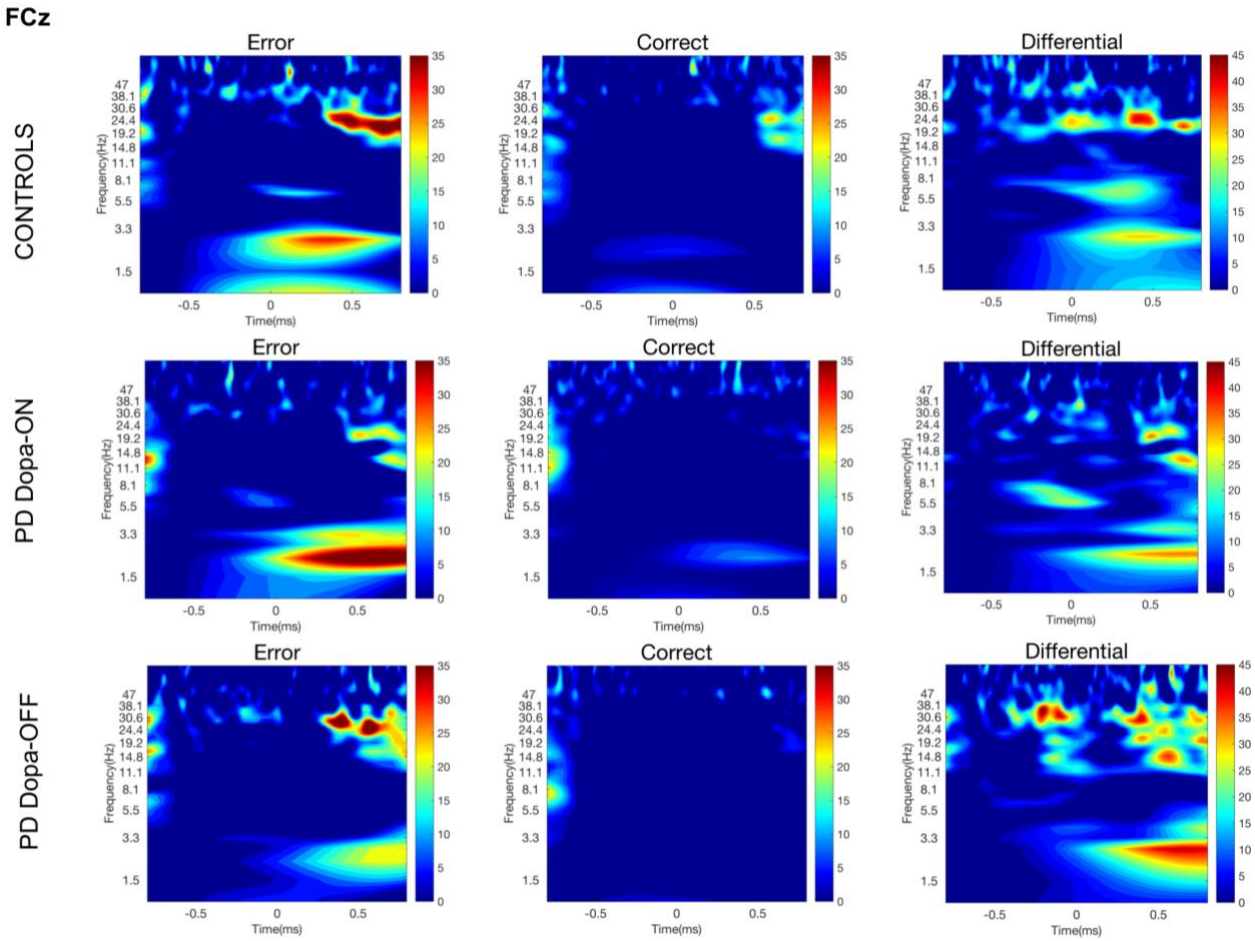


Figure 3. Time-frequency representation of Relative Power change (in %) with respect to the baseline for erroneous and correct conditions. The third column represents for each group the differential plot (erroneous minus correct actions). The end of avatar's limb-path deviation is set at 0ms. The graphs are displayed with logarithmic scale in the Y-axis.

ID	PM47	BADA N	BADA V	TMT_A	TMT_B	TMTB-A	WCSTcat	WCST_p	WCST_np	DIGIT SPAN BW	CORSI SPAN BW	FAS	F_CAT	F_ALT	ZOO_V1	STROOP_interferenza	CD	CDL
P01	34	30	28	61	131	70	6	1	0	5	4	38	48	36	8	19	10	70
P02	29	30	28	30	72	42	6	2	1	5	6	45	52	36	3	23	10	69
P03	32	30	29	51	99	48	6	1	0	4	4	38	35	25	2	20	10	68
P04	35	29	28	110	265	155	6	0	3	4	4	31	39	34	8	6	10	68
P05	35	27	27	36	133	97	6	0	0	5	5	31	42	32	7	22	11	70
P06	36	30	28	51	117	66	6	0	1	5	4	52	39	34	6	21	9	67
P07	28	28	26	86	326	240	4	5	9	4	3	40	34	22	4	15	7	70
P08	32	30	28	55	127	72	4	3	13	4	5	13	34	24	7	12	11	70

Table 1. Demographic and clinical data of the Parkinson patients.

ID	sex	età	scol	DIAGNOSI MCI	MMSE	MMPSE	PREYi	PREYd	RecH	RecFA	DIGIT SPAN FW	CORSI SPAN FW	Mpi	MPd	FIGREYc	FIGREYimm	FIGREYdiff
P01	M	83	8	Normale	29	31	51	11	12	1	6	4	6,8	5,6	35	21	20,5
P02	M	58	13	Normale	29	31	60	14	15	0	6	6	7,6	7,6	31	24	22
P03	M	77	13	Normale	29	28	48	11	15	0	6	4	5,4	5,5	33,5	19,5	15
P04	F	58	8	MCImd	28	31	30	6	13	4	4	5	6,4	6,4	36	5,5	11,5
P05	F	72	13	Normale	29	29	43	10	13	0	6	4	4,7	4,4	34	21	22
P06	F	70	13	Normale	30	31	58	14	14	0	6	5	6,9	6,8	33	18	20
P07	1	78	5	MCImd	29	25	23	6	13	1	5	4	6	5	32	1	1,5
P08	M	82	8	MCImd	29	25	35	5	10	3	5	4	3,3	3,3	36	21,5	0

Table 1. Demographic and clinical data of the Parkinson patients.

Chapter 6 General discussion

To continuously monitor the outcome of the own and others' actions is essential for goal-directed behavior. The ability to detect errors in behavior allows to derive appropriate strategies (e.g. post-error adaptation), learn from the contextual regularities and keep action performance as close to the optimum as possible (Ullsperger et al., 2104). The aim of this thesis was to extend our knowledge on error detection, focusing on some specific issues. In particular the aims of the studies included here, relied on an experimental paradigm (viz. passive observation of reach-to-grasp actions in 1PP) to i) disentangle the electrocortical signatures associated to goal violation and event rarity (Chapter 3); ii) verify the integrity of the error monitoring system in patients with hemispheric brain damage and diagnosis of Apraxia (Chapter 4); iii) investigate the alteration of the monitoring system in patients with dopaminergic loss – i.e. Parkinson's patients – as well as examine the role of the dopaminergic treatment in reaction to errors (Chapter 5). Finally, as an appendix to the main structure of the thesis we investigated the cortical activity of wheelchair elite basketball players during the anticipation of free shots (Chapter 7, Appendix). Taken together our results allow some interesting considerations that may lead to future research.

Errors and experience

In Chapter 3 we manipulated the probability of observing wrong actions to investigate whether stimulus expectation or goal violation modulate the reaction to errors. Results showed that an observed goal error (the *action slip*) triggers the activity of the performance monitoring system even when erroneous actions, which are, typically, rare events, occur more often than correct actions and thus are not salient because of their rarity. In this kind of paradigm, the observed action was a very simple action, which is generally easy to accomplish in every-day life; therefore, a successful outcome from the reaching movement might be expected from naïve observer. Consequently, a wrong

execution of that simple action – despite our experimental probability manipulation - might still represent a salient event, which elicit the typical signatures of cognitive control.

Indeed, a priori expectations are rather critical in any reaction to events (Friston, 2010; Koul, Soriano, Tversky, Becchio, Cavallo, 2019). In a recent study, MEG was used to explore the neural activity during probability-dependent action perception in areas pivotal for causal inference (i.e. TPJ), using bowling action animations. The findings show that our brains make predictive models of causal events, integrating top-down predictions based on previous events with bottom-up sensory information about the action currently being perceived. They show that beta and gamma signals in these regions were directly modulated by action probabilities (van Pelt, Heil, Kwisthout, Ondobaka, van Rooij, Bekkering, 2016); in that study, differently from ours, the observed actions were difficult to accomplish (at least if the observer is not an expert bowling striker!). Life-long exposure to certain facts indeed shape our a-priori expectations, thus our flexibility to adapt to unpredicted situations. This is also confirmed by a recent issue (Yon, De Lange, Press, 2018), titled 'The Predictive Brain as a stubborn scientist', highlighting how some predictions/expectations, despite external evidence, are hard to change. Concerning this, in a study on toddlers by the Bekkering's group, a significantly stronger motor activation was found - indicated by a stronger mu desynchronization over central electrodes - during the observation of extraordinary rather than ordinary actions (Stapel, Hunnius, van Elk, Bekkering, 2010). These ideas are also in line with previous evidence showing that motor experience influences motor simulation (Gallese, Fadiga, Fogassi, Rizzolatti, 1996; Braukmann et al., 2017), contributing on generating predictions about actions we observe (Kilner, Friston, Frith, 2007). The motor experience and familiarity have shown to play a crucial role in sport expertise, which shape the brain reactivity and proactivity to events (Yellow et al., 2009; Makris, Urgesi, 2014; Ridderinkhof et al., 2014). This evidence has also been partially provided by our study in the wheelchair basketball players (Appendix), which showed a different cortical activity in the time-domain, during the observation of basketball shots in three groups of people characterized by diverse range of expertise.

In our study of Chapter 3 we cannot directly disentangle in which measure it is the visual or the motor experience that contribute to the way the participant experienced the action error. However, the fact that a strong activity is elicited to the occurrence of an error, as a goal mismatch despite probability, still suggests how previous experience might play a crucial role.

The multifaced features of the error-monitoring system

The diverse studies in this thesis highlighted a multifaced nature of the error-monitoring system. Most of the evidence come from the studies in Chapter 4 and Chapter 5, in which we tested the integrity of the error-monitoring system in two very different pathologies, respectively Ideomotor Apraxia and Parkinson's Disease, characterized by diverse cognitive and motor deficits.

In both the study on Apraxic patients and the one on Parkinson's patients, we did not find an oERN in response to errors. In the Parkinson's patients however an oPe was still elicited. The presence of the oPe but the absence of the oERN suggest a dissociation between these two cortical potentials during error monitoring and processing. This interpretation would correspond with a number of previous studies suggesting that these two potentials reflect different processes of the monitoring system, which might be complementary, but which do not necessarily depend on each other (Flanker task: Di Gregorio, Maier and Steinhauser, 2018; digit entering task: Hewig et al., 2011; Woodman, 2010). For example, by using a Flanker task with varying levels of target letters masking, Di Gregorio and colleagues (2018) recently demonstrated that a Pe can be elicited by errors in the absence of a preceding ERN, suggesting that we might be observing two independent monitoring processes. Recent studies which tried to disentangle the role of ERN and Pe, suggested that the ERN seems not to be necessary to the emergence of the Pe and viceversa. Steinhauser and colleagues (2017) in a study applied Multivariate pattern analyses (MVPA) on action responses during a Flanker task. In this task, ERN and mid-frontal theta activity seems to rely on the same mechanisms and be elicited by the same events, namely the ones in which an error is detected and these systems code for the need of behavioral adjustments. Differently, the Pe might reflect the conscious evaluation of errors which

may derive from different source of information (Steinhauser, Maier, Steinhauser, 2017). Others suggested that the Pe might reflect the evaluation of evidence in working memory, thus representing a gradual constant updating and accumulation of evidence (Wessel et al., 2012; di Gregorio et al., 2016; Donchin and Coles, 1988; Dehaene, Changeux, 2003). Still confounding explanations are raised on how the system that underlie the Pe is linked with the detection of an error, and the dissociative role of early and late Pe. The attempt to specifically disentangle the role of ERN/theta and Pe was not one of the direct objectives of the present studies, and other kind of paradigms with stimulus-masking procedures would be more suited to respond to this intriguing question.

Furthermore, not only the frontal but also the posterior parietal cortex has been implicated in the detection and correction mechanisms (i.e. tracking tasks; Grea et al., 2002; Desmurget et al., 1999; Moreau et al., under revision; Holroyd and Krigolson, 2006). Midfrontal regions have been in fact identified as a strong "hub" for information flow, measured through theta-band phase synchronization (Cohen, 2011). These theta-band oscillations support long-range connectivity between the frontal regions and the posterior-occipital ones and have been associated with error processing and reward. A similar idea has been suggested by the source reconstruction analyses in the Supplementary Material of the study in Chapter 3, where an increased central and posterior theta activity has been found at the occurrence of errors as well as from the functional connectivity results in the Apraxia Study (Chapter 4). In the Apraxia Study, A+ exhibited a decreased theta phase synchronization of both the fronto-parietal and fronto-frontal network, compared to H and A-. Interestingly, when the evoked activity was subtracted by the induced activity in the erroneous actions, and so - in other words - when the oERN was subtracted to the theta-activity, still in the erroneous actions there was a greater theta power than the correct ones (Pezzetta et al., 2018). This supports the idea that the ongoing theta activity is not only phase-locked to the event of interest. Another recent confirmation on the possible role of theta oscillations as 'hub' for information transfer came from a study by Vecchiato and colleagues (2018) in which increased theta activity was found during a driving-

simulator experiment. When the breaking was compared to the accelerating activity, a burst of theta power was observed approximately 800 ms before pedal pressure, suggesting that a motor conflict between the two task-switching activities might had occurred.

Researchers are still investigating to what extent the cognitive control functions operate consciously or unconsciously and which are the benefits of a brain that works at different hierarchical levels of awareness (Pavone, Marzi, & Girelli, 2009; Charles, Van Opstal, Marti, Dehaene, 2013). Ullsperger and Von Cramon (2006) investigated the role of frontostriatal circuits in error processing in 9 patients with focal basal ganglia lesion and 7 patients with lateral prefrontal cortex lesions. Findings showed that compared to healthy adults, those patients had reduced error signatures. Despite these electrophysiological abnormalities, most of the patients were still able to correct errors as suggested by the post-error adaptation. Only in those patients in which the lesions were also extended to other areas, the post-error correction was impaired. Similarly, in our study on Parkinson's patients, most of the times patients correctly reported whether they saw an error or a correct action, when they were explicitly asked to respond to catch-trial questions. This might seem an apparent paradox, why the damage of the error-monitoring network is not accompanied by behavioral deficits as well? In the paper from Ullsperger and Von Cramon (2006), authors suggested that plasticity might have occurred to functionally compensate the impairment or that error monitoring might operate in many ways and at several hierarchical levels, that together orchestrate an optimal motor behavior. In our case it seems that the dissociation of different feature characterizing the error monitoring system might reflect deficient process as well as still functioning ones.

Although studies on clinical populations have often relevant limitations due to low sample sizes and heterogeneity of patient's clinical picture - as it is also the case here -, the results of these researches open new interesting scenarios and suggest us how the investigation of the error monitoring in patients can provide valuable information. Notably, the understanding of the multiple faces of this complex system will help identify possible early correlates of the monitoring decline.

Why use the Virtual Reality instead of 2D scenarios?

During the last two decades, the use of virtual reality has becoming a new tool for the investigation of the human behavior and the brain (Tieri, Morone, Paulucci, Iosa, 2018). Indeed, many researchers interfaced VR with neuroimaging and neurophysiological techniques, as alternative to the traditional 2-D environment. Concerning the manipulations that we performed in our studies, recent evidence (Slater, Perez-Marcos, Ehrsson, 2008; Slater et al., 2010) suggests that the 1PP and visual appearance of the virtual body play a crucial role in eliciting the illusory sensation of owning the virtual body itself. Thus, participants not only observe the virtual actions from a first-person perspective, but they also observe a real-size moving body located in the very same spatial position of the participant. Immersive VR is able in fact to elicit a strong feeling of 'being physically present', allowing the user to respond in a realistic way to the virtual stimuli by eliciting physiological reactions as if the subject is physically situated in a real place. This is especially useful to investigate the body reaction to events in situations in which the real stimuli would be harmful for the participants. Fusaro and colleagues (2016), for example, using immersive VR studied the physiological reactivity to painful stimuli (needle penetrating the virtual hand embodied in 1PP), without actually delivering any real stimuli. As already suggested in Chapter 2, our previous studies demonstrate that: i) virtual first-person perspective is sufficient to embody the avatar without external boosting (e.g. visuo-tactile stimulation like in the case of virtual hand illusion; Tieri et al., 2015a); ii) experiencing a higher sense of embodiment elicited greater theta power and oERN amplitude in response to errors; Pavone et al., 2016; Pezzetta et al., 2018).

In the studies of the thesis, we did not perform a direct comparison of the brain signatures of error detection when observed in virtual reality vs. traditional 2-D screens, so we cannot do straightforward comparisons. However, studies that directly compared brain activity in 2D vs. 3D scenarios found that the 3D scenario required a general allocation of greater resources for cognitive control, in comparison to 2D presentations (Slobounov, Ray, Johnson, Slobounov, Newell, 2015; Vecchiato et

al., 2015). Finally, all the events in our experimental paradigm occurred in a 3D real-size peripersonal space, an environment which may produce an enriched source of affordance towards the object (Costantini et al., 2007; Costantini et al., 2011; Pezzulo & Cisek, 2016) and thus maximize the salience of action errors. Future studies need to clarify how the brain excitability change when one embodies a virtual avatar in 1PP.

The dynamic nature of VR has also allowed researchers and therapists to successfully develop VR-based clinical assessments and treatments, for children and adults with brain damage or neuropsychological disease, even still greater evidence on this direction in required (Tieri et al., 2018).

Limits, future directions and ongoing projects

The results of the studies conducted so far open new avenues for studying the brain-related correlates during vicarious observation, error monitoring and action prediction.

First of all, future investigations need to replicate the results obtained so far, especially in the studies on pathological populations, by increasing the sample size. In Chapter 4 (Study on Apraxic population) we included a low number of participants due to restricted criteria of inclusion and difficulty in finding patients suitable for this protocol. Future studies will need to replicate this finding and verify the extension of the impairment of the error-monitoring system in apraxia.

The results of the studies conducted in the thesis, suggest a dynamic nature of the error – monitoring system, which changes with the aging brain. Previous studies already pointed out alterations in the post-error slowing, as well as a reduced amplitude of error-related components, compared to young adults (Nieuwenhuis et al., 2002; Hoffmann & Falkenstein, 2011). However, in the future it might be interesting to directly compare the cortical underpinnings of error monitoring in both young and old adults, in a simple task as the one adopted in the studies in the thesis, which eliminates some confounds linked with motor efficiency and speed. The combination of EEG and VR

offers indeed some advantages compared to the 2D scenarios (see section *'Why use the Virtual Reality instead of 2D scenarios?'*); recently studies are using the VR as a flexible and effective tool to assist rehabilitation trainings (i.e. balance, physical therapy) or test cognitive abilities in interactive conditions (i.e. spatial memory, cognitive control; Tieri et al., 2018). Promising uses of virtual reality also extend to neurofeedback studies (Cho et al., 2004) or the investigation of affordances (as action possibilities that the environment offers) along with the responsiveness to them in relation to the context (Rietveld, 2012; Turchet, 2015; Wokke, Knot, Fouad, & Ridderinkhof, 2016; Vecchiato et al., 2015; Vecchiato et al., 2018).

Regarding EEG data analyses, source analyses would be useful to estimate the cortical response to errors in pathological populations (in particular the Parkinson's patients), as they show a topographical scalp distribution rather different than healthy participants. Moreover, future investigation will need to confirm the results obtained with the connectivity at a scalp level in the apraxic patients and replicate them at a source level.

In the future we will also apply decoding techniques, which offer a number of advantages over univariate time-series analysis, and which takes into account the relationships between multiple variables - e.g. channels in EEG - instead of treating them as independent and measure relative activation strengths. Also, it offers the possibility to look at temporal generalization to characterize neural dynamics over time (King & Dehaene, 2014; Fahrenfort, Van Driel, Van Gaal, Olivers, 2018) or the use of representational similarity analysis to map different physiological measures over each other's.

On the same research line, we are also currently:

- designing a set of EEG-VR studies to investigate the cortical activity underlying the observation of movements, which can lead to a successful/unsuccessful outcome. In this study, rather than manipulating the percentage of event appearance in an experimental setup (as it was done in the study in Chapter 2), we will manipulate the a-priori expectation on

the possibility to succeed or not-succeed on a certain action based on different visual manipulations. Also, since the prediction of the possibility to succeed/not succeed in an action is also determined by the perceived difficulty of the action itself (Pezzullo et al., 2010; Van Pelt et al., 2016), we will manipulate the difficulty of the movement. I am the principal investigator of this project and is in collaboration with Gaetano Tieri, Duru Gun Ozkan, Prof. Salvatore M. Aglioti.

- designing a series of studies that investigate the effect of life-long a priori expectations and the influence of the instructions in the cortical response to 'errors'.
- performing an EEG-TMS-VR study, where 20 healthy participants are tested in three TMS-EEG sessions during which they observed through a head-mounted display a virtual right upper limb, overlapped to the real one, from a first-person perspective (1PP). This project is done to investigate the cortical excitability during the embodiment of a virtual arm. In two sessions they observe an arm that is fully attached to the virtual body while simultaneously motor areas (respectively in two different sessions) are TMS-stimulated; in another session the observed arm appeared detached from the virtual body. Oscillatory and source analyses are performed to investigate the real-time brain dynamics underpinning the embodiment of a virtual limb. This study is ongoing, and it is in collaboration with Elias Paolo Casula (principal investigator), Gaetano Tieri, Michele Maiella, Giacomo Koch, Prof. Salvatore M. Aglioti.
- performing an EEG study to investigate the roles of Motivation and Sense of Agency on the sense of control and its effect on error-related signatures. The aim of the project is to understand if the violation of different types of predictions - related respectively to the performed movement, or to the final objective of the action - give rise to a specific modulation of cortical activity (ERN/Pe and Theta). By using a task created by Villa et al., (2018), participants will execute simple movements (button press) following their free choice. After each movement participants observe the movement that they just performed

which might be delayed in time (acting on their Sense of Agency); the observed movement can be the same or not to the one executed by the participant. This study is ongoing, and it is in collaboration with Riccardo Villa (principal investigator), Giuseppina Porciello, Emmanuele Tidoni, Prof. Salvatore M. Aglioti.

- performing a behavioral study in which Parkinson patients are tested in their ON and OFF condition while they engage in a joint-action task. The aim of this study is to investigate how the dopaminergic system plays a role in facilitating rewarding interactions. This study is ongoing, and in collaboration with Vanessa Era (principal investigator), Matteo Candidi, Prof. Salvatore M. Aglioti.
- we are conducting an EEG experiment to decode the brain activity associated to motor imagery and motor attention during the observation of handball throws. To this aim, we will train a classifier (through Machine Learning techniques) to disentangle the two types of brain activities in non-expert players. This project is ongoing, I am the principal investigator and it is done in collaboration with Dilene Van Campen. Martijn Wokke, Prof. Salvatore Maria Aglioti and Prof. Richard Ridderinkhof.

APPENDIX

Action monitoring and predictive abilities in elite players

To predict upcoming events and detect errors in behavior is also crucial in social interactions, where one must correctly anticipate the behavior of the other person or infer their intention to act. Sports are a perfect example in which predictive processes take place. A reactive - rather than proactive - brain would not be fast enough to cope with external situations, like catching a ball or planning a counterattack (Aglioti, Cesari, Romani, Urgesi, 2008; Abreu, Macaluso, Azevedo, Cesari, Urgesi, Aglioti, 2012; Proverbio, Crotti, Manfredi, Adorni, Zani, 2012; Makris & Urgesi, 2014; van Pelt, Heil, Kwisthout, Ondobaka, van Rooij & Bekkering, 2016). Theories on predictive processing support the idea that the brain constantly updates the internal system, combinig information from bottom-up and top-down streams (Clark, 2013; Friston, 2014). These ideas are consistent also with the principles and mechanisms of perception–action coordination laid out in a recent integrative theoretical framework (IMPPACT; Ridderikhof, 2014), according to which the brain engages forward models to generate expectations and test their correctness.

Previous evidence in sport, as in music, showed that experts are faster and more precise at detecting errors in others' movement kinematics, within their domain of expertise (Candidi, Sacheli, Mega, & Aglioti, 2014; Panasiti, Pavone, & Aglioti, 2016; Makris & Urgesi, 2014). For example, elite basketball players can predict other players successful or unsuccessful free throws more rapidly and accurately based on their ability to read from body kinematics (Abreu et al., 2012). The possibility to study elite players has the advantage to observe how life-long acquirement of a particular ability may shape the way one observes own's and other's action during a sport related context. Importantly, the data collection is still ongoing and thus results have to be considered as preliminary.

Chapter 7 Predicting the fate of basketball throws: an EEG study in Wheelchair Basketball players

Abstract

Rapid detection of one's own and others' mistakes is a crucial ability in sport settings. Within action observation literature it was shown that athletes have differentiating neural activity when they observe domain-specific actions. Here we explored the behavioural and electrophysiological underpinnings of wheelchair athletes predicting the fate of free-throws performed by paraplegic athletes. Using EEG, we recorded 16 players from a professional team while they observed another player shooting and asked them to predict the outcome. Results showed a greater modulation of parietal EEG electrodes during the final part of the execution of the throw for expert players, compared to amateurs and naïve controls. Our data provide further support to the Action Observation Network literature in terms of showing differentiating activation for experts.

Introduction

Exercise for people with paraplegia is an excellent tool of physical rehabilitation, as well as for improving the psychological well-being (Di Russo et al., 2010); in high-level competition, expertise in open-skill sports improves response flexibility and performance in disabled athletes. Research on behavioural and neural underpinnings of expertise in sports as well as music show that accumulated experience enhances attunement to domain relevant actions (Weast, Walton, Chandler, Shockley, & Riley, 2014). For instance, expert pianists are faster and more precise at detecting errors in others' movement kinematics (Candidi, Sacheli, Mega, & Aglioti, 2014; Panasiti, Pavone, & Aglioti, 2016). In everyday life, reading body kinematics helps us predict intentions and others' action outcomes and to form an optimally accurate representation of our social surroundings. When we

execute actions or observe others' actions, the Action Observation Network (AON) comprised of premotor and inferior parietal regions becomes involved (Cross, Kraemer, Hamilton, Kelley, & Grafton, 2009; Gallese, Fadiga, Fogassi, & Rizzolatti, 1996). Findings suggest that action observation is supported by our own motor capacities. For instance, stimulation studies (TMS) showed corticospinal facilitation of the hand muscles measured via Motor Evoked Potential when observing grasping pictures with implied motion (Urgesi, Moro, Candidi & Aglioti, 2006).

Through EEG research, it was shown that familiarity of the observed actions modulates the involvement of AON (di Nota, Chartrand, Levkov, Siegmund & Desouza, 2017). Behavioural as well as neural activity from experts indicate specific enhancement in processing relevant information associated with the domain of expertise (Abreu et al., 2012; Calvo-Merino, Grèzes, Glaser, Passingham, & Haggard, 2006; Makris & Urgesi, 2014). For instance, elite basketball players can predict successful free throws more rapidly and accurately based on cues from body kinematics as reflected in the corticospinal facilitation difference between expert and novice groups, during the observation of successful and unsuccessful basket shots (Aglioti, Cesari, Romani, & Urgesi, 2008). Furthermore, experts focus on different parts or moments of the observed action compared to novices, and they focus on different perceptual visual cues (Ridderinkhof & Brass, 2015). For example, expert basketball players can detect deception from kinematics and postural cues, unlike novices (Fujii, Shinya, Yamashita, Kouzaki, & Oda, 2014; Sebanz & Shiffrar, 2009). Cues from body kinematics are so important to experts that when part of body kinematics is disguised, it reduces the experts' accuracy to the level of novices (Rowe Dr., Horswill, Kronvall-Parkinson, Poulter, & McKenna, 2009). Furthermore, electroencephalographic studies (EEG) highlighted a larger N400 during the perception of incorrect execution in both basketball players (Proverbio, Crotti, Manfredi, Adorni, & Zani, 2012) and expert dancers (Orlandi, Zani, & Proverbio, 2017). Complementary findings suggest that difference in the neural activity that relates to experience can be unique to sensorimotor areas: expert tennis players have greater accuracy in anticipating the outcome of tennis related action and

greater event related desynchronization in mu (8-13 Hz) and beta (14-30 Hz) frequency bands, that are associated with the activation of the AON (Denis, Rowe, Williams, & Milne, 2017).

In the current study, we focused on wheelchair basketball athletes. Wheelchair basketball, just like standard basketball, is an open-skill sport where the environment changes constantly and requires rapid execution and adaption. In Wheelchair Basketball, athletes are functionally classified between 1 (most severe disability) and 4 (least severe disability) according to the level of trunk movement and stability (De Lira et al., 2010; Jr et al., 1997). The functional classification of the players is balanced in opposing teams during the game, in order to achieve comparable levels of physical ability across the competing teams. The relationships among physical characteristics, performance, and functional ability are indeed strictly related; for example, the ability to shoot the basket from a wider range of distances and the circumference of the upper arm are related to the success in scoring, and there are overlaps of performance in all classes (Cavedon, Zancanaro, & Milanese, 2015; Malone, Gervais, & Steadward, 2002).

Our paradigm focused on the action prediction from body kinematics. We expected the EEG correlates of elite wheelchair basketball players to discriminate whether a basketball shot will be successful or unsuccessful. To test this, we asked the elite Santa Lucia Wheelchair Basketball team to observe the videos of another player and predict the outcome. We tested experts' wheelchair basketball players, amateur's wheelchair basketball players and a naïve group as controls. Furthermore, having confidence ratings as an additional material provides insights in to how much metacognition the different groups might have about their own performance in each trial.

Methods

Participants

The study was approved by the local Ethics Committee at the Fondazione Santa Lucia Research Hospital (Rome, Italy), and followed the ethical standards of the Declaration of Helsinki. The elite players were recruited from the Santa Lucia Wheelchair Basketball Team in Rome. The

sample consisted of 16 players, of which 10 players (10 Male, age: mean=35.1 years, ± SD=8.39; years of expertise: mean= 14.79 years, ± SD=9.35) from the A Team and 6 players (6 Male, age: mean=21.3 years, ± SD=1.63; expertise: mean= 2.16 years, ± SD=2.11) from the B Team. All players were paraplegic and used wheelchair (injuries: thoracic-back injury, paralysis or amputation of two limbs), except two players who could walk short distances with the aid of crutches, and one that could walk with prosthetic legs. Twenty-two controls were recruited from La Sapienza, University of Rome. Three participants were excluded due to technical reasons; therefore, EEG analyses were conducted on a total sample of 19 naïve participants (5 Male, 14 Female; Age = 27.16, SD = 5.8) and 16 elite players (10 experts, 6 amateurs). All participants had normal or corrected-to-normal vision and did not report head trauma or psychiatric disorder. One player from the B Team was left handed. All participants were screened with Beck Depression Inventory as per the exclusion criteria, due to depressions effect on sensitivity to errors (Olvet, & Hajcak, 2008); no participants were excluded.

Stimulus selection

The stimuli are comprised of video recordings of a wheelchair basketball player of the Santa Lucia Wheelchair Basketball Team (Figure 1B). The videos were recorded from a sagittal viewpoint. The videos display the shooting execution and end on the first frame of the ball leaving the hand.

Each trial lasted approximately 8 seconds. Each video started with the wheelchair basketball player, holding the ball for 1895 ms on average (SD = 63.2). The movement of the actor started 789 ms on average before the video ended (SD= 170.9). The execution of the throw itself lasted approximately 80 ms (SD = 22.6), where the player extended the arm, closed the wrist and let go of the ball. During the baseline part of the videos (mean = 1105.5 ms, SD = 185 ms), the player was seated with the ball at hand with a slight rocking movement. The baseline part of the videos was validated to make sure that the kinematics were uninformative by asking 8 naïve participants to try to guess the outcome of the actions. The participants performed at chance level, and they were not

included in the actual study. This pilot helped to ensure the neutrality of the baseline part of the stimuli.

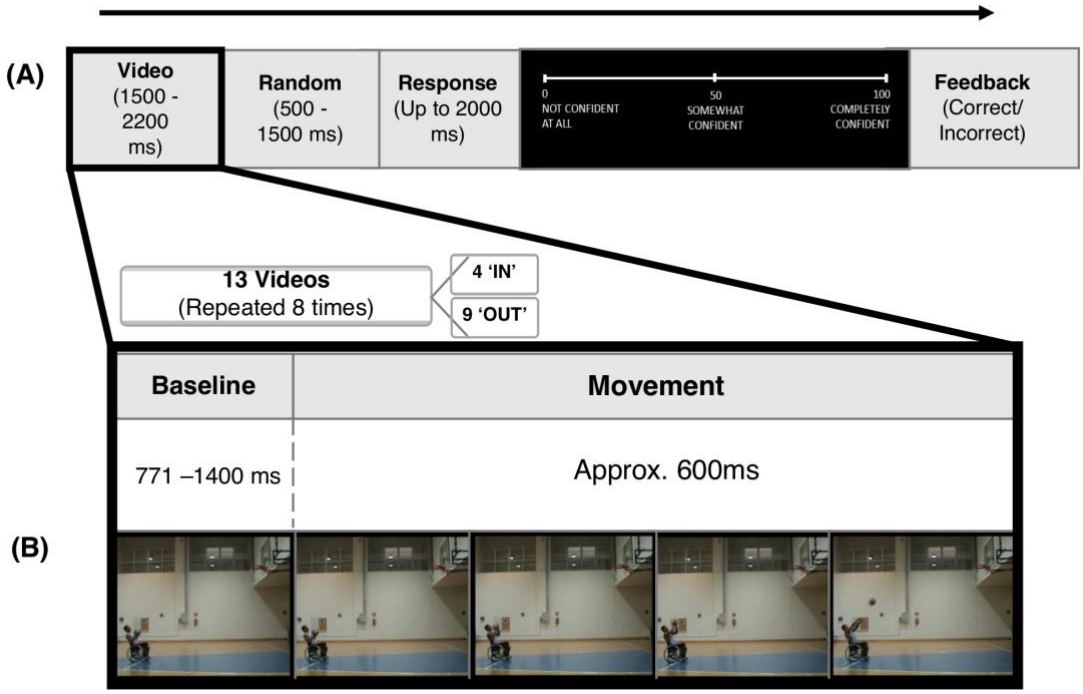


Figure 1 (A) Procedure (B) A representation of the videos, first, middle and last frames of the video

Procedure

Participants were seated comfortably in front of a PC. Before the experiment, the participants completed the practice phase and became familiar with the task (6 trials: 3 IN, 3 OUT). A total of 208 trials were delivered in 4 sessions with 3 breaks. Each session included 52 videos comprised of 26 free throws repeated twice. The duration of one trial lasted 8 seconds, one session was approximately 8 minutes, and the full task duration was approximately 35 minutes. Initially, we used 2 players in the videos, one with Point 1 classification and other with Point 4. However, 5 players recognized the Point 4 player in the video, so to avoid familiarity effects we decided to discard data from this condition. The videos were shown with the proportion of 30% "IN" and 70% "OUT". Only the data from 104 videos of Point 1 player were considered during the analysis. They were required to predict

whether the ball was going to be “IN” or “OUT”. The responses were recorded with pressing either left or right arrow buttons for “IN” and “OUT”.

Participants were instructed to keep their muscles relaxed as they watched the videos. They started the task by pressing the space bar. Each trial began with a fixation cross-placed on the location of the player, and participants were instructed to fix their gaze to this cross, and the player’s body throughout the trial. The videos were delivered in random order. After each video, there was a black screen (range: 500-1500 ms), followed by the response screen (Please see Figure 1A for the trial sequence). After their response, the participants rated how confident they were in their response in a Visual Analog Scale (VAS) from 0 to 100. Each trial ended with a feedback (correct or incorrect). Information regarding their expertise (i.e. number of hours/years of practice) was annotated. For analyses we used a 2X3 factorial design comprised of (*i*) Video Outcome: “IN” and “OUT”, and (*ii*) Group: “A Team”, “B Team”, “Controls”. Data collection is still ongoing and results have to be considered as preliminary.

EEG recording

The triggers containing timing information for EEG recording were sent part via the photodiode, a device that delivers triggers activated with a white patch placed on the bottom right corner of each video at the last frame. Time 0 was fixed at the end of the video. EEG signals were recorded by using a Neuroscan SynAmpsRT amplifiers system (Compumedics, ltd) with 60 electrode elastic headband (Electro-Cap, International, Eaton, OH) positioned according to the international 10-10 system. The signals were acquired from channels: Fp1, Fpz, Fp2, AF3, F4, F7, F5, F3, F1, F4, FC2, FC3, FC1, P1, P2, C4, C6, T8, TP7, CP5, CP3, CP1, CP2, CP2, CP4, CP6, TP8, P7, P5, P3, P4, P6, P8, PO7, PO3, AF7, PO4, AF8, PO4, PO8, O1, Oz, O2, FT7 and FT8. The ground electrode was positioned on the scalp ALF derivation, while the reference electrodes were applied to the left ear (digital reference) and right (physical reference) lobes. The Horizontal Electro-Oculogram (HEOG) was recorded bilaterally, and Vertical (VOEG) was electrodes positioned under the left eye. The

signal was recorded with an online low-band filter 0.01-200 Hz and digitized at a sampling rate of 1000 Hz. Impedances were maintained under 5 KΩ by applying gel-electrodes (ElectroGel) to all electrodes. After the data collection, the raw files were downsampled to the rate of 500 Hz. Blink artifacts were removed by visual inspection of the Independent component analysis (ICA; Jung et al., 2000) applied to the continuous EEG signal (Mean = 3.6 components, range 1:6), using the Matlab toolbox EEGLab (Delorme & Makeig, 2004).

Analysis

Behavioral Analysis

Statistical analyses for the behavioral data were performed with SPSS (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). Mean accuracy rates were calculated for each group. We ran a mixed-design ANOVA with video type and group as within and between groups' factors, respectively. The accuracy data guided trial selection in our EEG analysis. For the EEG analysis, we included only the trials that participants were able to guess accurately as "IN" or "OUT". We have also determined that the accuracy rates were clear of perceptual bias: in order to assess whether participants might have a bias towards giving "IN" or "OUT" response more often, we ran a signal detection analysis. Within the signal detection analysis, we have grouped the two player groups (A and B Teams) together. We also controlled for the learning effect, measuring the accuracy rates throughout each block of trials, and the performance did not improve in time.

We ran a Pearson Chi-Square test between the High vs Low metacognition regarding the answers of the participants. The metacognitive accuracy rates were calculated by obtaining one value (1 -High, 0 -Low) for each trial from the confidence ratings that matched or did not match the correct and incorrect answers. If a correct response was given with a below 50% confidence rating, it was categorized as "Low metacognitive accuracy", if an incorrect response was given with a below 50% confidence rating, it was categorized as "High metacognitive accuracy". These values were used to get a percentage of metacognition for each participant and used to analyze the group differences.

Time domain Analysis

Time domain analysis were performed using the Brain Vision Analyzer 1.05 software (Brain-Products, GmbH). The data were band-pass filtered to 0.5-30Hz. The signal was epoched in wide windows of 2200 ms, from -1500 to + 700 ms relative to stimulus offset. Epochs were time locked to the end of the players' movement and were baseline corrected with a chosen interval of 200 ms during the baseline period of the videos, when the player sits still (from -1400 to -1200 ms relative to stimulus offset). Only correctly, predicted trials were included in the analysis. Each epoch was visually inspected for artifacts and the residual epochs with eye blinks or epochs exceeding -100/+100μV amplitude were manually removed. A total of 918 "IN" and 2176 "OUT" trials were analyzed for (~ 86.7% of total collected trials). Bad channels were interpolated only when necessary (3 channels were interpolated in twelve subjects, but were not included in the analysis; Perrin, Pernier, Bertrand, & Echallier, 1989). ERPs were calculated with the *erpR* package (Arcara & Petrova, 2014) in R Studio (R Core Team, 2014). The Analysis of Variance were conducted with the *ez* package (Lawrence, 2013). In line with previous literature we focused our analyses on the parietal area (Jin et al., 2011), and mainly on the electrode Pz.

Results

Behavioural Results

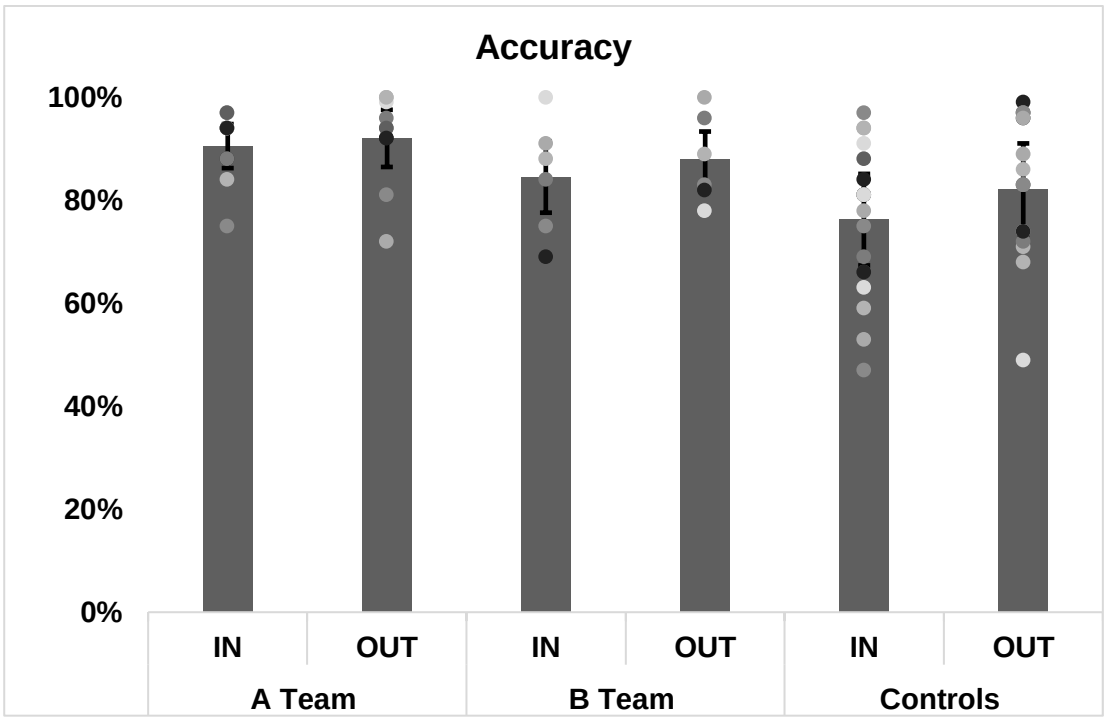


Figure 2 Accuracy rates of each group in each condition. The dots represent each subject (some dots overlap with each-other in the figure)

A Team was significantly better than Controls (p<.001), but no other main effect or interactions were observed. Figure 2 shows the mean accuracy rates for each group and each condition. The mean accuracy for "IN" videos were 90.5% for A Team, 84.5% for the B Team and 76.21% for the controls (SD = 0.07, 0.11, 0.14; respectively). In "OUT" videos A Team was accurate in 92% of the trials, B Team 88% and Controls 82.2% accurate (SD = 0.09, 0.09, 0.14; respectively). There was a significant main effect of group on accuracy rates $F(2,32)=6.279$, $p=.005$. However, there was no significant main effect of the video outcome ("IN" or "OUT"), $F(1,32)=1.348$, $p=.254$, or a significant interaction between the video outcome and group $F(1,32)=.240$, $p=.788$. Bonferroni corrected pairwise comparisons revealed that the A Team was significantly more accurate in predicting the outcome of the basket than the Controls, regardless of the video type (Mean = 12.1%, $p=.0045$, $d' = 1.42$, $r=.58$). However, B Team did not differ from the A Team or the Controls (Mean = 5%, $p=.855$, Mean = 7%, $p=.3$; respectively).

Players had lower rates of false alarms and higher rates of correct rejects compared to the control groups $F(1, 33) = 11.2$, $p = .002$. According to the signal detection analysis, overall perceptual sensitivity of the players was significantly higher ($d'_{\mathbf{Player}} = 2.95$, $SE = 1.00 > d'_{\mathbf{Controls}} = 1.81$, $SE = .74$), and neither group had any bias for giving either "IN" or "OUT" responses more often than one another, due to the stimulus frequency.

There was a significant association between the type of group and metacognition $\chi^2(2) = 32.85$, $p < .001$. Cramer's V value (.095) suggest that type of group has a small effect on the metacognition

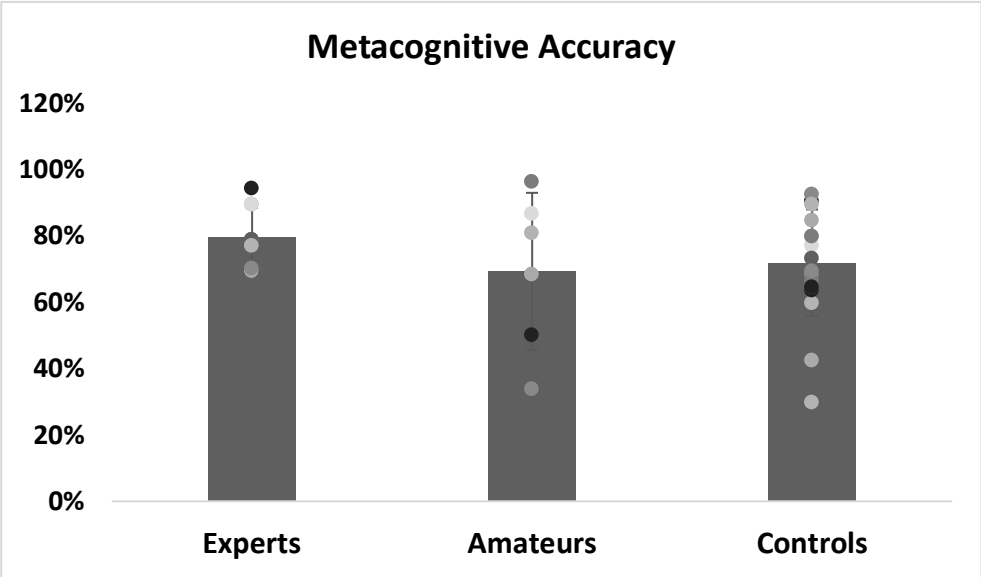


Figure 3 Scatter-bar plots that show the distribution of metacognition. Y- axes represents the metacognition (%) calculated from the confidence ratings and their actual performance. The dots represent the single observations (some dots overlap with each-other in the figure).

regarding their own performance. A Team had the metacognition of 79.5%, whereas B Team had 69.2% and Controls had 70.5%. Figure 3 shows the scatter-bar plots of each group.

Time Domain Results

For the Time Domain analysis, we chose the window of time according to the part of the videos that carry most of the information about the throwing, that is the last 100 ms of each video, where the player bends the wrist and lets the ball go. We did not analyze the signals once the video

stops, as it was not the focus of the current study. The repeated measures ANOVA revealed a significant main effect of group on the time series values $F(2,32)=3.67$, $p=.004$. There was also a significant interaction of group and video outcome $F(2,32)=4.10$, $p=.025$. However, there was no significant main effect of video outcome $F(2,32)=.7$, $p=.407$. FDR corrected multiple comparisons revealed the pattern of interactions. A Team was significantly more negative in amplitude than B Team in "IN" videos ($Mean_{Difference}=-4.17$, $p=.023$), but not in "OUT" videos ($Mean_{Difference}=-2.87$, $p=.078$). A Team was also significantly more negative in amplitude than

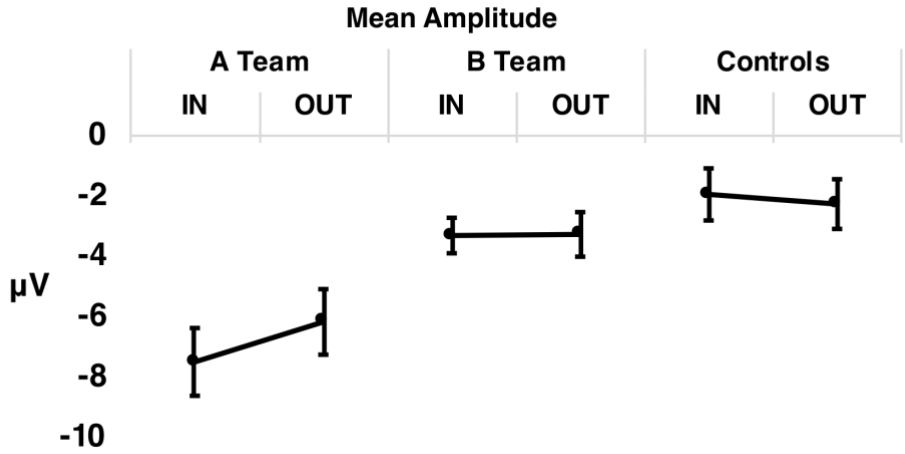


Figure 4 Mean amplitude values of electrode Pz between -100-0 ms (0 ms represents the end of the action, when the ball is released by the player's hand). The values are reported for each group (A Team, B Team and Controls) and condition (IN, OUT).

controls both in "IN" and "OUT" videos ($Mean_{Difference}=-5.52$, $p=.011$, $Mean_{Difference}=-3.9$, $p=.025$; respectively). The analysis did not survive Bonferroni correction. Figure 4 (B) shows the scalp distributions of the average signal (-100ms to 0).

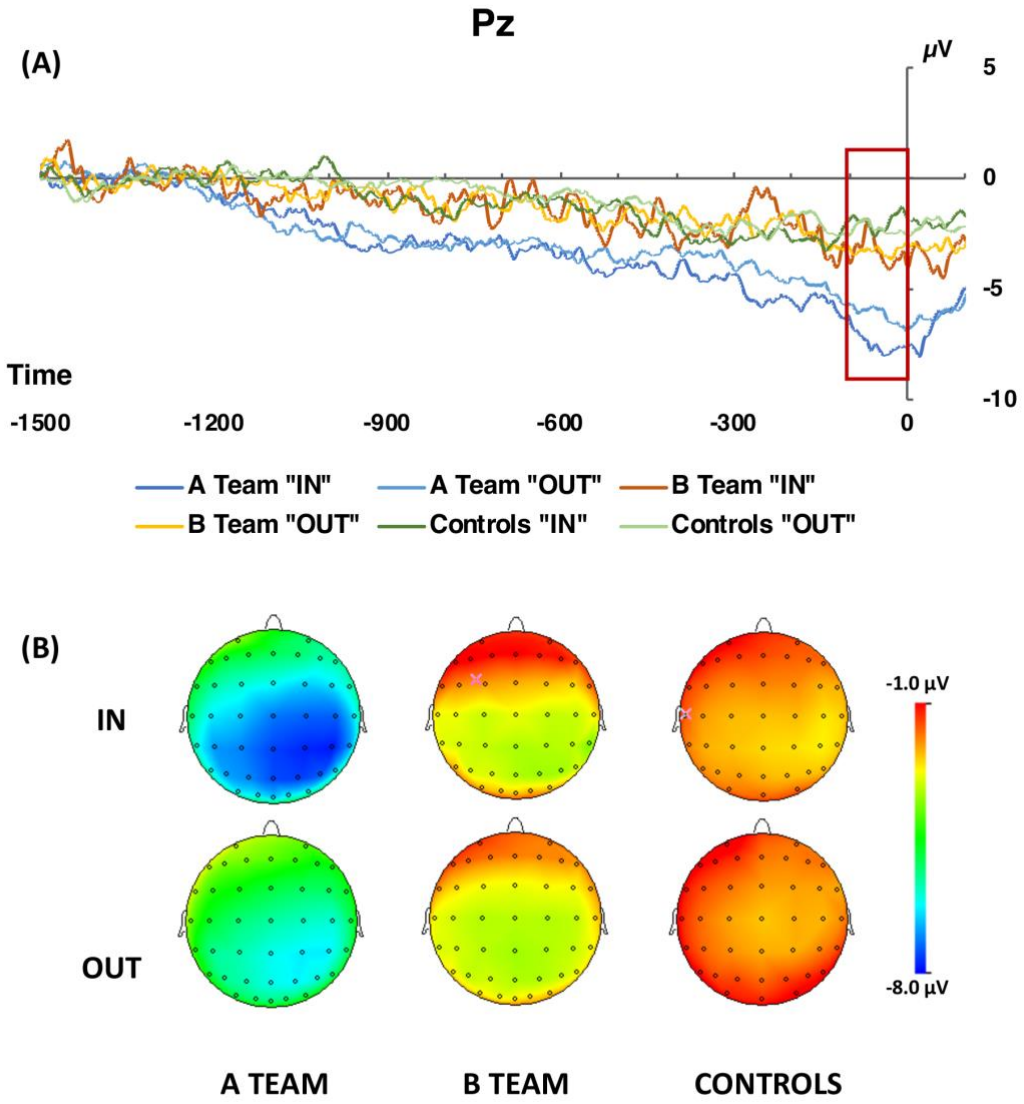


Figure 5 (A) Time domain signals – The area marked with red specifies the 100ms time window considered for the statistical analysis. 0 ms represents the end of the video, when the ball is released by the player's hand. Different colors highligt the groups and experimental conditions (B) Topographical voltage distribution for IN and OUT conditions in the three groups.

Discussion

Experts differ from novices in relying on more refined sources of information when it comes to navigating within their domain of expertise. Consequently, they are better able to predict and adapt to sudden changes. In the present study, we aimed at identifying EEG neural signatures in the time domain during action observation in an expert population. To do this, we tested the elite athletes from the Santa Lucia Wheelchair Basketball team (A Team), the new recruits that have recently started with the team (B Team), and complete novices (Controls). All subjects were asked to predict the outcome of free throw videos. This task allowed us to examine neural activity with respect to domain specific actions. Indeed, our data show a different pattern for expert athletes (A Team) in comparison to the amateurs (B Team) and novices, reflected in the negative amplitude during the part of the action that conveys the crucial information in a basket shot (Figure 5).

Accuracy rates

As expected, A Team (with an average of 14 years of expertise across players) was significantly more accurate than both B Team and the Controls. B Team had higher accuracy than the controls, but this difference did not reach significance. It should be noted that the success rate across all three groups of participants is 85.6%. This shows that the shot outcome was relatively easy to predict in the videos. However, this also shows that expertise played a significant role in being constant in correctly detecting the fate of the basketball shots. In line with previous findings regarding motor expertise, we also show that the elite athletes were significantly more aware of their performance (as indicated by confidence ratings). This indicates that at a conscious level, the athletes were better able to assess whether their prediction was accurate, which might have implications on their proactive behavior in a real game setting.

Neuroelectrical signals

The main hypothesis was that neurophysiological correlates of domain-specific action anticipation through observation would be modulated in experts. Echoing the accuracy results, the A Team had significantly stronger parietal EEG negative amplitude compared to both other groups (B Team and Controls) during the key point of the observed throw: when the wrist closes to complete the shot. In Aglioti et al., 2008, it was shown that expert basketball players were focusing on the kinematics of the shot while the expert watchers (i.e. non-players) used later cues like the ball trajectory in order to reach successful predictions. By occluding the ball trajectory, the present study builds up on Aglioti and collaborators' finding, and highlights EEG correlates associated with the reading from kinematics (i.e. arm and wrist movements). While experts show a significant negative deflection in the parietal regions during the observation of the kinematics of a basketball shot, novices and controls do not differ. Similar to our results, it was recently shown that subtle intention-specific kinematic information can be decoded from a network that involves parietal regions (Koul et al., 2018). Furthermore, during the observation of the moving body, parietal region of expert dancers was shown to contribute to the integrating kinesthetic perception with the representation of the dance syntax (Bachrach, Jola, & Pallier, 2016). In our study, we focused our analyses on the electrode-level, which prevents direct comparison to neuroimaging studies that specify the parietal region in the context of expertise, nevertheless, our results are in line with studies that have shown different brain activation for experts, with various imaging techniques and tasks. In our study, we have shown a negativity in the posterior electrodes during the crucial moments of action cues for anticipation, in a basketball shot. Successful action integration and prediction allows experts for quicker and better adjustment in situations that require their expertise (Hack, Memmert, & Rupp, 2009; Wu et al., 2013). Experts are therefore better in action execution during unexpected situations that may arise in the

domain of their expertise, and show different AON activation during action perception tasks (Wang, Yang, Moreau, Muggleton, & Tu, 2017; Wang & Tu, 2017).

Anticipation or outcome prediction can be manipulated statistically, by expectations that are set within the specific task requirements or by the need to rely on others movement (Heil, Kwisthout, van Pelt, van Rooij, & Bekkering, 2018; Pezzetta et al. 2018; Moreau et al., under review). However, different neural signatures can be observed with anticipation in statistically unpredictable situations. Furthermore, action anticipation based on biological kinematics can have an impact on neural activation. Experts simulate the observed domain specific action (Senna, Bolognini, & Maravita, 2014; Tomasino, Guatto, Rumiati, & Fabbro, 2012; Ridderinkhof et al., 2014). While the heterogeneity of athletes' physical ability as well as the low number of participants impedes addressing straightforward questions regarding the effects of actual physical ability/disability on AON network, it still provides a setting in which physical expertise can be studied. Wheelchair basketball requires skills acquired with more difficulty than regular basketball, and perceptual-motor training (obtained by a visual constraint that forced participants to use target information as late as possible) has a positive impact on future successful shooting percentages (Oudejans, Janssen, Heubers, Ruitenbeek, & Ruitenbeek, 2012).

There is much interest in how expertise affects not just the behaviour but also plasticity in the brain, and research in this area has valuable impact on understanding the mechanisms underlying of learning and skill acquisition and the rewiring of the brain after an acquired motor disability.

Future Directions

The relationship between expertise and AON engagement has been modelled within different frameworks. Recently, a quadratic relationship between increasing familiarity and the accuracy of predictions was proposed (Gardner, Aglinskas, & Cross, 2017). Gardner and his colleagues trained participants in guitar movements. They demonstrated that the BOLD activity in the AON to be present during both highly familiar and highly unfamiliar observed actions, former, due to more accurate

predictions, latter due to continuous updating. It would be beneficial for future EEG/MEG studies to examine how the parietal negativity during domain specific action observation due to sports expertise might be affected with a manipulation that could result in a quadratic relationship. In our study, we compared subjects that are experts, amateurs and completely naïve controls. We aimed to describe the expertise related observational properties, but we did not induced a task expertise within our paradigm. It is necessary for future studies to address questions regarding how motor skill learning occurs, or more specifically, how motor expertise acquisition makes changes in the brain (Ossmy & Mukamel, 2018), to have on-line information about training induced brain plasticity. One limitation in our study was that our video stimuli did not provide the most ecological setting. Future research would benefit from immersive virtual-reality environments to provide more realistic and controlled setups (Pavone et al., 2016) to target specific features of action observation in experts.

Importantly, the data collection is still ongoing and thus results have to be considered as preliminary (a post-hoc analysis was performed posteriori, and a power of 0.80 is associated for the main effects, and a power of 0.70 for the interaction). Future data will need to confirm the results obtained so far. We are also recruiting gender/age matched paraplegic individuals, with no expertise in basketball, as a further control group.

Conclusions

The neural activity related to expertise has had substantial amount of attention in recent years. In this study, we aimed to describe the EEG signals relating to predictive observation in wheelchair basketball expertise. Our data support and extend the literature by demonstrating more negative activity in elite athletes, significant in the moment where the expert players focus on the crucial information for them.

References

Aarsland, D., Zaccai, J., & Brayne, C. (2005). A systematic review of prevalence studies of dementia in Parkinson's disease. Movement disorders, 20(10), 1255-1263.

Abbruzzese, G., Avanzino, L., Marchese, R., & Pelosin, E. (2015). Action Observation and Motor Imagery: Innovative Cognitive Tools in the Rehabilitation of Parkinson's Disease. *Parkinson's disease*.

Abreu, A. M., Macaluso, E., Azevedo, R. T., Cesari, P., Urgesi, C., & Aglioti, S. M. (2012). Action anticipation beyond the action observation network: A functional magnetic resonance imaging study in expert basketball players. European Journal of Neuroscience, 35(10), 1646–1654.

Aglioti, S. M., Cesari, P., Romani, M., & Urgesi, C. (2008). Action anticipation and motor resonance in elite basketball players. Nature Neuroscience, 11(9), 1109–1116.

Akam, T., & Kullmann, D. M. (2014). Oscillatory multiplexing of population codes for selective communication in the mammalian brain. Nature Reviews Neuroscience, 15(2), 111.

Alain, C., McNeely, H. E., He, Y., Christensen, B. K., & West, R. (2002). Neurophysiological evidence of error-monitoring deficits in patients with schizophrenia. Cerebral Cortex, 12(8), 840-846.

Alexander WH, Brown JW. Medial prefrontal cortex as an action-outcome predictor. Nat Neurosci 14: 1338–1344, 2011. doi:10.1038/nn.2921.

Ambrosini, E., & Vallesi, A. (2016). Asymmetry in prefrontal resting-state EEG spectral power underlies individual differences in phasic and sustained cognitive control. Neuroimage, 124, 843-857.

Angela, J. Y., & Dayan, P. (2005). Uncertainty, neuromodulation, and attention. Neuron, 46(4), 681-692.

Appollonio, I., Leone, M., Isella, V., Piamarta, F., Consoli, T., Villa, M. L., ... & Nichelli, P. (2005). The Frontal Assessment Battery (FAB): normative values in an Italian population sample. Neurological Sciences, 26(2), 108-116.

Arcara G, Petrova A. erpR (2014). Event-related potentials (ERP) analysis, graphics and utility functions (version 0.2.0).

Arrighi P, Bonfiglio L, Minichilli F, Cantore N, Carboncini MC, Piccotti E, Rossi B, Andre P. (2016) EEG theta dynamics within frontal and parietal cortices for error processing during reaching movements in a prism adaptation study altering visuo-motor predictive planning. PLoS One 11: e0150265.

Avenanti A, Bolognini N, Maravita A, Aglioti SM (2007). Somatic and motor components of action simulation. Curr Biol 17: 2129–2135

Avenanti, A., Candidi, M., & Urgesi, C. (2013). Vicarious motor activation during action perception: beyond correlational evidence. Frontiers in human neuroscience, 7, 185.

Babiloni, C., Binetti, G., Cassarino, A., Dal Forno, G., Del Percio, C., Ferreri, F., ... & Lanuzza, B. (2006). Sources of cortical rhythms in adults during physiological aging: a multicentric EEG study. Human brain mapping, 27(2), 162-172.

Babiloni, C., Del Percio, C., Iacoboni, M., Infarinato, F., Lizio, R., Marzano, N., ... & Eusebi, F. (2008). Golf putt outcomes are predicted by sensorimotor cerebral EEG rhythms. The Journal of Physiology, 586(1), 131-139.

Bachrach, A., Jola, C., & Pallier, C. (2016). Neuronal bases of structural coherence in contemporary dance observation. NeuroImage, 124, 464–472.

Bates AT, Patel TP, Liddle PF (2005). External behavior monitoring mirrors internal behavior monitoring error-related negativity for observed errors. J Psychophysiol 19: 281–288.

Bekkering H, de Bruijn ER, Cuijpers RH, Newman-Norlund R, Van Schie HT, Meulenbroek R. (2009) Joint action: neurocognitive mechanisms supporting human interaction. Top Cogn Sci 1: 340–352.

Benedek M, Schickel RJ, Jauk E, Fink A, Neubauer AC. (2014) Alpha power increases in right parietal cortex reflects focused internal attention. Neuropsychologia 56: 393–400.

Beste, C., Saft, C., Konrad, C., Andrich, J., Habbel, A., Schepers, I., ... & Falkenstein, M. (2008). Levels of error processing in Huntington's disease: A combined study using event-related potentials and voxel-based morphometry.*Human brain mapping*, 29(2), 121-130.

Beyer, M. K., Janvin, C. C., Larsen, J. P., & Aarsland, D. (2007). A magnetic resonance imaging study of patients with Parkinson's disease with mild cognitive impairment and dementia using voxel-based morphometry. *Journal of Neurology, Neurosurgery & Psychiatry*, 78(3), 254-259.

Bizzozero, I., Costato, D., Sala, S. D., Papagno, C., Spinnler, H., & Venneri, A. (2000). Upper and lower face apraxia: role of the right hemisphere. Brain, 123(11), 2213-2230.

Boldt, A., & Yeung, N. (2015). Shared neural markers of decision confidence and error detection. Journal of Neuroscience, 35(8), 3478-3484.

Botvinick, M. M., Braver, T. S., Barch, D. M., Carter, C. S., & Cohen, J. D. (2001). Conflict monitoring and cognitive control. Psychological review, 108(3), 624.

Braukmann, R., Bekkering, H., Hidding, M., Poljac, E., Buitelaar, J. K., & Hunnius, S. (2017). Predictability of action sub-steps modulates motor system activation during the observation of goal-directed actions. *Neuropsychologia*, *103*, 44-53.

Buxbaum, L. J., Johnson-Frey, S. H., & Bartlett-Williams, M. (2005). Deficient internal models for planning hand–object interactions in apraxia. Neuropsychologia, 43(6), 917-929.

Buxbaum, L. J., Shapiro, A. D., & Coslett, H. B. (2014). Reply: Apraxia: a gestural or a cognitive disorder? Brain, 138(3), e334-e334.

Calmels, C., Pichon, S., & Grèzes, J. (2014). Can we simulate an action that we temporarily cannot perform? Neurophysiologie Clinique, 44(5), 433–445.

Calvo-Merino, B., Grèzes, J., Glaser, D. E., Passingham, R. E., & Haggard, P. (2006). Seeing or Doing? Influence of Visual and Motor Familiarity in Action Observation. Current Biology, 16(19), 1905–1910.

Candidi, M., Sacheli, L. M., Era, V., Canzano, L., Tieri, G., & Aglioti, S. M. (2017). Come together: human–avatar on-line interactions boost joint-action performance in apraxic patients. Social cognitive and affective neuroscience, 12(11), 1793-1802.

Candidi, M., Sacheli, L. M., Mega, I., & Aglioti, S. M. (2014). Somatotopic mapping of piano fingering errors in sensorimotor experts: TMS studies in pianists and visually trained musically naïves. Cerebral Cortex, 24(2), 435–443.

Canzano, L., Scandola, M., Pernigo, S., Aglioti, S. M., & Moro, V. (2014). Anosognosia for apraxia: Experimental evidence for defective awareness of one's own bucco-facial gestures. Cortex, 61, 148-157.

Canzano, L., Scandola, M., Gobbetto, V., Moretto, G., D'Imperio, D., & Moro, V. (2016). The representation of objects in apraxia: from action execution to error awareness. Frontiers in human neuroscience, 10, 39.

Carp J, Compton RJ. Alpha power is influenced by performance errors. (2009) Psychophysiology 46: 336 –343.

Carter, C. S., Braver, T. S., Barch, D. M., Botvinick, M. M., Noll, D., & Cohen, J. D. (1998). Anterior cingulate cortex, error detection, and the online monitoring of performance. Science, 280(5364), 747-749.

Catani, M., & de Schotten, M. T. (2012). Atlas of human brain connections. Oxford University Press.

Cavanagh JF, Cohen MX, Allen JJ. Prelude to and resolution of an error: EEG phase synchrony reveals cognitive control dynamics during action monitoring. J Neurosci 29: 98–105.

Cavanagh JF, Frank MJ. (2014) Frontal theta as a mechanism for cognitive control. Trends Cogn Sci 18: 414–421.

Cavanagh JF, Zambrano-Vazquez L, Allen JJ. (2012) Theta lingua franca: a common mid-frontal substrate for action monitoring processes. Psychophysiology 49: 220–238.

Cavanagh, J. F., Frank, M. J., Klein, T. J., & Allen, J. J. (2010). Frontal theta links prediction errors to behavioral adaptation in reinforcement learning. Neuroimage, 49(4), 3198-3209.

Cavanagh, J. F., Kumar, P., Mueller, A. A., Richardson, S. P., & Mueen, A. (2018). Diminished EEG habituation to novel events effectively classifies Parkinson's patients. *Clinical Neurophysiology*, *129*(2), 409-418.

Cavanagh, J. F., & Shackman, A. J. (2015). Frontal midline theta reflects anxiety and cognitive control: meta-analytic evidence. Journal of Physiology-Paris, 109(1-3), 3-15.

Cavedon, V., Zancanaro, C., & Milanese, C. (2015). Physique and performance of young wheelchair basketball players in relation with classification. PLoS ONE, 10(11), 1–20. https://doi.org/10.1371/journal.pone.0143621

Chaudhuri, K. R., Healy, D. G., & Schapira, A. H. (2006). Non-motor symptoms of Parkinson's disease: diagnosis and management. The Lancet Neurology,5(3), 235-245.

Charles, L., Van Opstal, F., Marti, S., & Dehaene, S. (2013). Distinct brain mechanisms for conscious versus subliminal error detection. Neuroimage, 73, 80-94.

Cho, B. H., Kim, S., Shin, D. I., Lee, J. H., Min Lee, S., Young Kim, I., & Kim, S. I. (2004). Neurofeedback training with virtual reality for inattention and impulsiveness. Cyberpsychology & Behavior, 7(5), 519-526.

Cisek, P. (2007). Cortical mechanisms of action selection: the affordance competition hypothesis. Philosophical Transactions of the Royal Society B: Biological Sciences, 362(1485), 1585-1599.

Clark, A. (2013). Whatever next? Predictive brains, situated agents, and the future of cognitive science. Behavioral and brain *sciences*, *36*(3), 181-204.

Clayton MS, Yeung N, Cohen Kadosh R. (2015) The roles of cortical oscillations in sustained attention. Trends Cogn Sci 19: 188–195.

Cohen MX. (2014a). Analyzing Neural Time Series Data: Theory and Practice. Cambridge, MA: MIT Press, p. 600.

Cohen, M. X. (2014b). A neural microcircuit for cognitive conflict detection and signaling. Trends in neurosciences, 37(9), 480-490.

Cohen, M. X. (2011). Error-related medial frontal theta activity predicts cingulate-related structural connectivity. Neuroimage, 55(3), 1373-1383.

Cohen, M. X., & Cavanagh, J. F. (2011). Single-trial regression elucidates the role of prefrontal theta oscillations in response conflict. Frontiers in psychology, 2, 30.

Cohen, M. X., & Donner, T. H. (2013). Midfrontal conflict-related theta-band power reflects neural oscillations that predict behavior. Journal of Neurophysiology, 110(12), 2752-2763.

Cohen, M. X., Van Gaal, S., Ridderinkhof, K. R., & Lamme, V. (2009). Unconscious errors enhance prefrontal-occipital oscillatory synchrony. Frontiers in human neuroscience, 3, 54.

Conejero A, Guerra S, Abundis-Gutiérrez A, Rueda MR. (2018) Frontal theta activation associated with error detection in toddlers: influence of familial socioeconomic status. Dev Sci 21: e12494.

Cools, R. (2006). Dopaminergic modulation of cognitive function-implications for L-DOPA treatment in Parkinson's disease. *Neuroscience & Biobehavioral Reviews*, *30*(1), 1-23

Cools, R., & D'Esposito, M. (2011). Inverted-U–shaped dopamine actions on human working memory and cognitive control. Biological psychiatry, 69(12), e113-e125.

Cooper, R. P. (2007). Tool use and related errors in ideational apraxia: The quantitative simulation of patient error profiles. Cortex, 43(3), 319-337.

Corbetta M, Shulman GL. (2002) Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 3: 201–215.

Costa, A., Peppe, A., Dell'Agnello, G., Caltagirone, C., & Carlesimo, G. A. (2009). Dopamine and cognitive functioning in de novo subjects with Parkinson's disease: effects of pramipexole and pergolide on working memory. *Neuropsychologia*, *47*(5), 1374-1381.

Costantini M, Ambrosini E, Scorolli C, Borghi AM. (2011) When objects are close to me: affordances in the peripersonal space. Psychon Bull Rev 18: 302–308.

Costantini M, Ambrosini E, Tieri G, Sinigaglia C, Committeri G. (2010) Where does an object trigger an action? An investigation about affordances in space. Exp Brain Res 207: 95–103.

Cross, E. S., Kraemer, D. J. M., Hamilton, A. F. D. C., Kelley, W. M., & Grafton, S. T. (2009). Sensitivity of the action observation network to physical and observational learning. Cerebral Cortex, 19(2), 315–326.

Cruz-Neira C, Sandin DJ, DeFanti TA. Surround-screen projection- based virtual reality: the design and implementation of the CAVE. In: SIGGRAPH '93. Proceedings of the 20th Annual Conference on Computer Graphics and Interactive Techniques. New York: Association for Computing Machinery, 1993, p. 135–142.

Cubelli, R., Marchetti, C., Boscolo, G., & Della Sala, S. (2000). Cognition in action: Testing a model of limb apraxia. Brain and cognition, 44(2), 144-165.

Daitch, A. L., Sharma, M., Roland, J. L., Astafiev, S. V., Bundy, D. T., Gaona, C. M., ... & Corbetta, M. (2013). Frequency-specific mechanism links human brain networks for spatial attention. Proceedings of the National Academy of Sciences, 110(48), 19585-19590.

Dayan, P., & Yu, A. J. (2006). Phasic norepinephrine: a neural interrupt signal for unexpected events. Network: Computation in Neural Systems, 17(4), 335-350.

de Bruijn ER, Miedl SF, Bekkering H. (2011) How a co-actor's task affects monitoring of own errors: evidence from a social event-related potential study. Exp Brain Res 211: 397–404.

de Bruijn ER, Schubotz RI, Ullsperger M. (2007) An event-related potential study on the observation of erroneous everyday actions. Cogn Affect Behav Neurosci 7: 278–285.

de Bruijn ER, von Rhein DT. (2012) Is your error my concern? An event-related potential study on own and observed error detection in cooperation and competition. Front Neurosci 6: 8.

De Lira, C. A. B., Vancini, R. L., Minozzo, F. C., Sousa, B. S., Dubas, J. P., Andrade, M. S., … Da Silva, A. C. (2010). Relationship between aerobic and anaerobic parameters and functional classification in wheelchair basketball players. Scandinavian Journal of Medicine and Science in Sports, 20(4), 638–643.

De Renzi, E., & Lucchelli, F. (1988). Ideational apraxia. Brain, 111(5), 1173-1185

Debener S, Makeig S, Delorme A, Engel AK. (2005) What is novel in the novelty oddball paradigm? Functional significance of the novelty P3 event-related potential as revealed by independent component analysis. Brain Res 22: 309–321.

Dehaene, S., & Changeux, J. P. (2003). Neural mechanisms for access to consciousness. *The cognitive neurosciences III*.

Denis, D., Rowe, R., Williams, A. M., & Milne, E. (2017). The role of cortical sensorimotor oscillations in action anticipation. NeuroImage, 146(July 2016), 1102–1114.

Desmurget, M., Epstein, C. M., Turner, R. S., Prablanc, C., Alexander, G. E., & Grafton, S. T. (1999). Role of the posterior parietal cortex in updating reaching movements to a visual target. *Nature neuroscience*, *2*(6), 563.

Di Gregorio F, Steinhauser M, Maier ME. (2016) Error-related brain activity and error awareness in an error classification paradigm. Neuroimage 139: –210.

Di Gregorio, F., Maier, M. E., & Steinhauser, M. (2018). Errors can elicit an error positivity in the absence of an error negativity: Evidence for independent systems of human error monitoring. NeuroImage.

Nota, P. M., Chartrand, J. M., Levkov, G. R., Montefusco-Siegmund, R., & DeSouza, J. F. (2017). Experience-dependent modulation of alpha and beta during action observation and motor imagery. BMC neuroscience, 18(1), 28.

Di Russo, F., Bultrini, A., Brunelli, S., Delussu, A. S., Polidori, L., Taddei, F., … Spinelli, D. (2010). Benefits of Sports Participation for Executive Function in Disabled Athletes. Journal of Neurotrauma, 27(12), 2309–2319.

Dirnberger, G., & Jahanshahi, M. (2013). Executive dysfunction in Parkinson's disease: A review. Journal of neuropsychology, 7(2), 193-224.

Donchin E, Coles MG. (1988) Is the P300 component a manifestation of context updating? Behav Brain Sci 11: 357–374.

Donnarumma F, Costantini M, Ambrosini E, Friston K, Pezzulo G. (2017) Action perception as hypothesis testing. Cortex 89: 45–60.

Doyle, L. M. F., Kühn, A. A., Hariz, M., Kupsch, A., Schneider, G. H., & Brown, P. (2005). Levodopa-induced modulation of subthalamic beta oscillations during self-paced movements in patients with Parkinson's disease. *European Journal of Neuroscience*, *21*(5), 1403-1412.

Dürschmid, S., Edwards, E., Reichert, C., Dewar, C., Hinrichs, H., Heinze, H. J., ... & Knight, R. T. (2016). Hierarchy of prediction errors for auditory events in human temporal and frontal cortex. Proceedings of the National Academy of Sciences, 113(24), 6755-6760.

Endrass, T., Reuter, B., & Kathmann, N. (2007). ERP correlates of conscious error recognition: aware and unaware errors in an antisaccade task. European Journal of Neuroscience, 26(6), 1714-1720.

Endrass, T., Schuermann, B., Kaufmann, C., Spielberg, R., Kniesche, R., & Kathmann, N. (2010). Performance monitoring and error significance in patients with obsessive-compulsive disorder. Biological psychology, 84(2), 257-263.

Engel, A. K., & Fries, P. (2010). Beta-band oscillations—signalling the status quo?. *Current opinion in neurobiology*, *20*(2), 156-165.

Ernst, B., & Steinhauser, M. (2017). Top-down control over feedback processing: The probability of valid feedback affects feedback-related brain activity. Brain and cognition, 115, 33-40.

Fahrenfort, J. J., Van Driel, J., Van Gaal, S., & Olivers, C. N. (2018). From ERPs to MVPA using the Amsterdam Decoding and Modeling toolbox (ADAM). Frontiers in neuroscience, 12.

Falkenstein M, Hohnsbein J, Hoormann J, Blanke L. (1991) Effects of crossmodal divided attention on late ERP components. II. Error processing in choice reaction tasks. Electroencephalogr Clin Neurophysiol 78: 447–455.

Falkenstein, M., Hielscher, H., Dziobek, I., Schwarzenau, P., Hoormann, J., Sundermann, B., & Hohnsbein, J. (2001). Action monitoring, error detection, and the basal ganglia: an ERP study. *Neuroreport*, 12(1), 157-161.

Falkenstein, M., Hoormann, J., Christ, S., & Hohnsbein, J. (2000). ERP components on reaction errors and their functional significance: a tutorial. Biological psychology, 51(2-3), 87-107.

Farooqui, A. A., Bhutani, N., Kulashekhar, S., Behari, M., Goel, V., & Murthy, A. (2011). Impaired conflict monitoring in Parkinson's disease patients during an oculomotor redirect task. *Experimental brain research*, 208(1), 1-10.

Faul F, Erdfelder E, Lang AG, Buchner A. (2007) G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 39: 175–191.

Fischer AG, Klein TA, Ullsperger M. (2017) Comparing the error-related negativity across groups: The impact of error- and trial-number differences. Psychophysiology 54: 998–1009.

Fischer AG, Ullsperger M. (2013) Real and fictive outcomes are processed differently but converge on a common adaptive mechanism. Neuron 79: 1243–1255.

Fonken, Y. M., Rieger, J. W., Tzvi, E., Crone, N. E., Chang, E., Parvizi, J., ... & Krämer, U. M. (2016). Frontal and motor cortex contributions to response inhibition: evidence from electrocorticography. Journal of neurophysiology, 115(4), 2224-2236.

Foti D, Weinberg A, Bernat EM, Proudfit GH. (2015) Anterior cingulate activity to monetary loss and basal ganglia activity to monetary gain uniquely contribute to the feedback negativity. Clin Neurophysiol 126: 1338–1347.

Fries, P. (2005). A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. Trends in cognitive sciences, 9(10), 474-480.

Fries, P. (2015). Rhythms for cognition: communication through coherence. Neuron, 88(1), 220-235.

Friston, K. (2010). The free-energy principle: a unified brain theory?. *Nature reviews neuroscience*, *11*(2), 127.

Fujii, K., Shinya, M., Yamashita, D., Kouzaki, M., & Oda, S. (2014). Anticipation by basketball defenders: An explanation based on the three-dimensional inverted pendulum model. European Journal of Sport Science, 14(6), 538–546.

Fusaro M, Tieri G, Aglioti SM. (2016) Seeing pain and pleasure on self and others: behavioural and psychophysiological reactivity in immersive virtual reality. J Neurophysiol 116: 2656–2662.

Gallese, V., Fadiga, L., Fogassi, L., & Rizzolatti, G. (1996). Action recognition in the premotor cortex. Brain : A Journal of Neurology, 119 (Pt 2(2), 593–609.

Gardner, T., Aglinskas, A., & Cross, E. S. (2017). Using guitar learning to probe the Action Observation Network's response to visuomotor familiarity. NeuroImage, 156(April), 174–189.

Gardner, T., Goulden, N., & Cross, E. S. (2015). Dynamic Modulation of the Action Observation Network by Movement Familiarity. Journal of Neuroscience, 35(4), 1561–1572.

Garofalo S, Timmermann C, Battaglia S, Maier ME, di Pellegrino G. (2017) Mediofrontal negativity signals unexpected timing of salient outcomes. JCogn Neurosci 29: 718–727.

Gehring WJ, Goss B, Coles MG, Meyer DE, Donchin E. A neural system for error detection and compensation. Psychol Sci 4: 385–390, 1993. doi:10.1111/j.1467-9280.1993.tb00586.x.

Gehring WJ, Liu Y, Orr JM, Carp J. The error-related negativity (ERN/Ne). In: The Oxford Handbook of Event-Related Potentials, edited by Kappenman ES, Luck SJ. New York: Oxford University Press, 2012.

Gehring, W. J., & Knight, R. T. (2000). Prefrontal–cingulate interactions in action monitoring. Nature neuroscience, 3(5), 516.

Gillies M, Spanlang B. (2010) Comparing and evaluating real time character engines for virtual environments. Presence (Camb) 19: 95–117.

Gréa, H., Pisella, L., Rossetti, Y., Desmurget, M., Tilikete, C., Grafton, S., ... & Vighetto, A. (2002). A lesion of the posterior parietal cortex disrupts on-line adjustments during aiming movements. *Neuropsychologia*, *40*(13), 2471-2480.

Gregoriou, G. G., Gotts, S. J., Zhou, H., & Desimone, R. (2009). High-frequency, long-range coupling between prefrontal and visual cortex during attention. science, 324(5931), 1207-1210.

Hack, J., Memmert, D., & Rupp, A. (2009). Attentional mechanisms in sports via brain-electrical event-related potentials. Research Quarterly for Exercise and Sport, 80(4), 727–738.

Hajcak G, Moser JS, Yeung N, Simons RF. (2005) On the ERN and the significance of errors. Psychophysiology 42: 151–160.

Hajihosseini A, Holroyd CB. (2013) Frontal midline theta and N200 amplitude reflect complementary information about expectancy and outcome evaluation. Psychophysiology 50: 550–562.

Halsband, U., Schmitt, J., Weyers, M., Binkofski, F., Grützner, G., & Freund, H. J. (2001). Recognition and imitation of pantomimed motor acts after unilateral parietal and premotor lesions: A perspective on apraxia. Neuropsychologia, 39(2), 200-216.

Hanslmayr, S., Pastötter, B., Bäuml, K. H., Gruber, S., Wimber, M., & Klimesch, W. (2008). The electrophysiological dynamics of interference during the Stroop task. Journal of Cognitive Neuroscience, 20(2), 215-225.

Heil, L., Kwisthout, J., van Pelt, S., van Rooij, I., & Bekkering, H. (2018). One wouldn't expect an expert bowler to hit only two pins: Hierarchical predictive processing of agent-caused events. Quarterly Journal of Experimental Psychology, 174702181775210.

Helfrich, R. F., & Knight, R. T. (2016). Oscillatory dynamics of prefrontal cognitive control. Trends in cognitive sciences, 20(12), 916-930.

Heremans, E., Feys, P., Nieuwboer, A., Vercruysse, S., Vandenberghe, W., Sharma, N., & Helsen, W. (2011). Motor imagery ability in patients with early-and mid-stage Parkinson disease. *Neurorehabilitation and neural repair*, 25(2), 168-177.

Hewig, J., Coles, M. G., Trippe, R. H., Hecht, H., & Miltner, W. H. (2011). Dissociation of Pe and ERN/Ne in the conscious recognition of an error. *Psychophysiology*, *48*(10), 1390-1396.

Holroyd CB, Coles MG. (2002) The neural basis of human error processing: reinforcement learning, dopamine, and the error-related negativity. Psychol Rev 109: 679–709.

Holroyd CB, Hajcak G, Larsen JT. (2006) The good, the bad and the neutral: electrophysiological responses to feedback stimuli. Brain Res 1105: 93–101.

Holroyd, C. B., Praamstra, P., Plat, E., & Coles, M. G. (2002). Spared error-related potentials in mild to moderate Parkinson's disease. *Neuropsychologia*, *40*(12), 2116-2124.

Huang W, Alem L, Tecchia F. HandsIn3D: supporting remote guidance with immersive virtual environments. In: Lecture Notes in Computer Science (including subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics). Berlin: Springer, 2013, vol. 8117, p. 70–77.

Hughes, A. J., Daniel, S. E., Kilford, L., & Lees, A. J. (1992). Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *Journal of Neurology, Neurosurgery & Psychiatry*, *55*(3), 181-184.

Janssen DJ, Poljac E, Bekkering H. (2016) Binary sensitivity of theta activity for gain and loss when monitoring parametric prediction errors. Soc Cogn Affect Neurosci 11: 1280–1289.

Jessup RK, Busemeyer JR, Brown JW. (2010) Error effects in anterior cingulate cortex reverse when error likelihood is high. J Neurosci 30: 3467–3472.

Jin, H., Xu, G., Zhang, J. X., Gao, H., Ye, Z., Wang, P., … Lin, C. De. (2011). Event-related potential effects of superior action anticipation in professional badminton players. Neuroscience Letters, 492(3), 139–144.

Joch M, Hegele M, Maurer H, Müller H, Maurer LK. (2017) Brain negativity as an indicator of predictive error processing: the contribution of visual action effect monitoring. J Neurophysiol 118: 486–495.

Jocham,G. & Ullsperger, M. (2009). Neuropharmacology of performance monitoring. Neuroscience & Biobehavioral Reviews, 33(1), 48-60.

Jocham, G., Klein, T. A., & Ullsperger, M. (2011). Dopamine-mediated reinforcement learning signals in the striatum and ventromedial prefrontal cortex underlie value-based choices. Journal of Neuroscience, 31(5), 1606-1613.

Jr, F. M. M., Bracken, M. B., Creasey, G., Jr, J. F. D., Donovan, W. H., Ducker, T. B., … Young, W.

(1997). International Standards for Neurological and Functional Classification of Spinal Cord Injury. Spinal Cord, 35(5), 266–274.

Jung TP, Makeig S, Westerfield M, Townsend J, Courchesne E, Sejnowski TJ. (2010) Removal of eye activity artifacts from visual event-related potentials in normal and clinical subjects. Clin Neurophysiol 111: 1745–1758.

Jurkiewicz, M. T., Gaetz, W. C., Bostan, A. C., & Cheyne, D. (2006). Post-movement beta rebound is generated in motor cortex: evidence from neuromagnetic recordings. *Neuroimage*, *32*(3), 1281-1289.

Keysers, C., & Gazzola, V. (2014). Hebbian learning and predictive mirror neurons for actions, sensations and emotions. Phil. Trans. R. Soc. B, 369(1644), 20130175.

Kilner, J. M. (2011). More than one pathway to action understanding. Trends in cognitive sciences, 15(8), 352-357.

Kilner JM, Friston KJ, Frith CD. (2007) Predictive coding: an account of the mirror neuron system. Cogn Process 8: 159–166.

Kilner, J. M., Friston, K. J., & Frith, C. D. (2007). Predictive coding: an account of the mirror neuron system. Cognitive processing, 8(3), 159-166.

Kilteni, K., Groten, R., & Slater, M. (2012). The sense of embodiment in virtual reality. Presence: Teleoperators and Virtual Environments, 21(4), 373-387.

Kim, Y. C., Han, S. W., Alberico, S. L., Ruggiero, R. N., De Corte, B., Chen, K. H., & Narayanan, N. S. (2017). Optogenetic stimulation of frontal D1 neurons compensates for impaired temporal control of action in dopamine-depleted mice. Current Biology, 27(1), 39-47.

Marti, S., King, J. R., & Dehaene, S. (2015). Time-resolved decoding of two processing chains during dual-task interference. Neuron, 88(6), 1297-1307.

Klein, T. A., Endrass, T., Kathmann, N., Neumann, J., von Cramon, D. Y., & Ullsperger, M. (2007). Neural correlates of error awareness. Neuroimage, 34(4), 1774-1781.

Klimesch W. (2012) Alpha-band oscillations, attention, and controlled access to stored information. Trends Cogn Sci 16: 606–617.

Klimesch, W. (1999). EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. Brain research reviews, 29(2-3), 169-195.

Koban L, Pourtois G. Brain systems underlying the affective and social monitoring of actions: an integrative review. Neurosci Biobehav Rev 46, P1: 71–84, 2014. doi: 10.1016/j .neubiorev .2014.02.0 14.

Koban, L., Pourtois, G., Vocat, R., & Vuilleumier, P. (2010). When your errors make me lose or win: event-related potentials to observed errors of cooperators and competitors. Social Neuroscience, 5(4), 360-374.

Kobza S, Bellebaum C. Mediofrontal event-related potentials following observed actions reflect an action prediction error. Eur J Neurosci 37: 1435–1440, 2013.

Koelewijn T, van Schie HT, Bekkering H, Oostenveld R, Jensen O. (2008) Motor-cortical beta oscillations are modulated by correctness of observed action. Neuroimage 40: 767–775.

Kopp, B., Lange, F., Howe, J., & Wessel, K. (2014). Age-related changes in neural recruitment for cognitive control. Brain and cognition, 85, 209-219.

Koul, A., Cavallo, A., Cauda, F., Costa, T., Diano, M., Pontil, M., & Becchio, C. (2018). Action Observation Areas Represent Intentions From Subtle Kinematic Features. Cerebral Cortex (New York, N.Y. : 1991), (May), 1–8.

Koul, A., Soriano, M., Tversky, B., Becchio, C., & Cavallo, A. (2019). The kinematics that you do not expect: Integrating prior information and kinematics to understand intentions. Cognition, 182, 213-219.

Krigolson OE, Holroyd CB. (2006) Evidence for hierarchical error processing in the human brain. Neuroscience 137: 13–17.

Lachaux, J. P., Rodriguez, E., Martinerie, J., & Varela, F. J. (1999). Measuring phase synchrony in brain signals. Human brain mapping, 8(4), 194-208.

Larson, M. J., Clayson, P. E., Keith, C. M., Hunt, I. J., Hedges, D. W., Nielsen, B. L., & Call, V. R. (2016). Cognitive control adjustments in healthy older and younger adults: Conflict adaptation, the error-related negativity (ERN), and evidence of generalized decline with age. Biological psychology, 115, 50-63.

Lawrence MA. ez: Easy Analysis and Visualization of Factorial Experiments (version 4.2–2), 2013. https://CRAN.R-project.org/package!ez. Luck SJ. An Introduction to Event-Related Potential Technique. Cambridge, MA: MIT Press, 2005.

Luck SJ, Kappenman ES (Editors). The Oxford Handbook of Event-Related Potential Components. New York: Oxford University Press, 2011.

Luu P, Tucker DM, Makeig S. (2004) Frontal midline theta and the error-related negativity: neurophysiological mechanisms of action regulation. Clin Neurophysiol 115: 1821–1835.

Luzzatti, C., Willmes, K., & De Bleser, R. (1996). Aachener aphasie test: versione italiana. Firenze: Organizzazioni Speciali.

Maier ME, di Pellegrino G, Steinhauser M. Enhanced error-related negativity on flanker errors: error expectancy or error significance? Psychophysiology 49: 899–908, 2012. doi:10.1111/j.1469-8986.2012.01373.x.

Maier ME, Steinhauser M. (2016) Error significance but not error expectancy predicts error-related negativities for different error types. Behav Brain Res 297: 259–267.

Makris, S., & Urgesi, C. (2014). Neural underpinnings of superior action prediction abilities in soccer players. Social cognitive and affective neuroscience, 10(3), 342-351.

Malone, L. a, Gervais, P. L., & Steadward, R. D. (2002). Shooting mechanics related to player classification and free throw success in wheelchair basketball. Journal of Rehabilitation Research and Development, 39(6), 701–709. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/17943672

Maris, E., & Oostenveld, R. (2007). Nonparametric statistical testing of EEG-and MEG-data. Journal of neuroscience methods, 164(1), 177-190.

Mas-Herrero E, Marco-Pallarés J. (2014) Frontal theta oscillatory activity is a common mechanism for the computation of unexpected outcomes and learning rate. J Cogn Neurosci 26: 447–458.

Masina, F., Vallesi, A., Di Rosa, E., Semenzato, L., & Mapelli, D. (2018). Possible role of dorsolateral prefrontal cortex in error awareness: single-pulse TMS evidence. Frontiers in neuroscience, 12, 179.

Mathewson, K. J., Dywan, J., & Segalowitz, S. J. (2005). Brain bases of error-related ERPs as influenced by age and task. Biological psychology, 70(2), 88-104.

Mazaheri A, Nieuwenhuis IL, van Dijk H, Jensen O. (2009) Prestimulus alpha and mu activity predicts failure to inhibit motor responses. Hum Brain Mapp 30: 1791–1800.

Meyer M, Braukmann R, Stapel JC, Bekkering H, Hunnius S. (2016) Monitoring others' errors: The role of the motor system in early childhood and adulthood. Br J Dev Psychol 34: 66–85

Miller, E. K. (2000). The prefontral cortex and cognitive control. Nature reviews neuroscience, 1(1), 59.

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. Annual review of neuroscience, 24(1), 167-202.

Miltner, W. H., Brauer, J., Hecht, H., Trippe, R., & Coles, M. G. (2004). Parallel brain activity for self-generated and observed errors.

Moreau, Q., Tieri, G., Era, V., Candidi, M., & Aglioti, S. M. (2018). Frontal and occipito-temporal Theta activity as marker of error monitoring in Human-Avatar joint performance. BioRxiv Preprint.

Munneke, G. J., Nap, T. S., Schippers, E. E., & Cohen, M. X. (2015). A statistical comparison of EEG time-and time–frequency domain representations of error processing. Brain research, 1618, 222-230.

Nácher, V., Ledberg, A., Deco, G., & Romo, R. (2013). Coherent delta-band oscillations between cortical areas correlate with decision making. Proceedings of the National Academy of Sciences, 110(37), 15085-15090.

Navarro-Cebrian A, Knight RT, Kayser AS. (2016) Frontal monitoring and parietal evidence: mechanisms of error correction. J Cogn Neurosci 28: 1166–1177.

Nieuwenhuis S, Ridderinkhof KR, Blom J, Band GP, Kok A. (2001) Error-related brain potentials are differentially related to awareness of response errors: evidence from an antisaccade task. Psychophysiology 38: 752–760.

Nieuwenhuis, S., Ridderinkhof, K. R., Talsma, D., Coles, M. G., Holroyd, C. B., Kok, A., & Van der Molen, M. W. (2002). A computational account of altered error processing in older age: dopamine and the error-related negativity. Cognitive, Affective, & Behavioral Neuroscience, 2(1), 19-36.

Nieuwenhuis S, Schweizer TS, Mars RB, Botvinick MM, Hajcak G. (2007) Error-likelihood prediction in the medial frontal cortex: a critical evaluation. Cereb Cortex 17: 1570–1581.

Nieuwenhuis, S., Aston-Jones, G., & Cohen, J. D. (2005). Decision making, the P3, and the locus coeruleus--norepinephrine system. Psychological bulletin, 131(4), 510.

Nolte, G., Bai, O., Wheaton, L., Mari, Z., Vorbach, S., & Hallett, M. (2004). Identifying true brain interaction from EEG data using the imaginary part of coherency. Clinical neurophysiology, 115(10), 2292-2307.

Notebaert W, Houtman F, Opstal FV, Gevers W, Fias W, Verguts T. (2009) Post-error slowing: an orienting account. Cognition 111: 275–279.

Núñez Castellar E, Kühn S, Fias W, Notebaert W. (2010) Outcome expectancy and not accuracy determines posterror slowing: ERP support. Cogn Affect Behav Neurosci 10: 270–278.

Oliveira FTP, McDonald JJ, Goodman D. (2007) Performance monitoring in the anterior cingulate is not all error related: expectancy deviation and the representation of action-outcome associations. J Cogn Neurosci 19: 1994–2004.

Oostenveld, R., Fries, P., Maris, E., & Schoffelen, J. M. (2011). FieldTrip: open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. Computational intelligence and neuroscience, 2011, 1.

Orlandi, A., Zani, A., & Proverbio, A. M. (2017). Dance expertise modulates visual sensitivity to complex biological movements. Neuropsychologia, 104(August), 168–181.

Ossmy, O., & Mukamel, R. (2018). Perception as a Route for Motor Skill Learning: Perspectives from Neuroscience. Neuroscience, 382, 144–153.

Oswal, A., Brown, P., and Litvak, V. (2013). Synchronized neural oscillations and the pathophysiology of Parkinson's disease. Curr. Opin. Neurol. 26, 662–670.

Oudejans, R. R. D., Janssen, T. W. J., Heubers, S., Ruitenbeek, J. R. J. A. C., & Ruitenbeek, J. R. J. A. C. (2012). Training visual control in wheelchair basketball shooting. Research Quarterly for Exercise and Sport, 83(3), 464–469.

Overbeek TJ, Nieuwenhuis S, Ridderinkhof KR. (2005) Dissociable components of error processing: on the functional significance of the Pe vis-a-vis the ERN/Ne. J Psychophysiol 19: 319–329.

Ozkan, D. G., & Pezzetta, R. (2017). Predictive monitoring of actions, EEG recordings in virtual reality. *Journal of neurophysiology*.

Padrao G, Gonzalez-Franco M, Sanchez-Vives MV, Slater M, Rodriguez-Fornells A. (2016) Violating body movement semantics: Neural signatures of self-generated and external-generated errors. Neuroimage 124: 147–156.

Panasiti MS, Pavone EF, Aglioti SM. (2016) Electrocortical signatures of detecting errors in the actions of others: An EEG study in pianists, non-pianist musicians and musically naïve people. Neuroscience 318: 104–113.

Panasiti MS, Porciello G, Aglioti SM. (2017) The bright and the dark sides of motor simulation. Neuropsychologia 105: 92–100.

Parker, K. L., Chen, K. H., Kingyon, J. R., Cavanagh, J. F., & Narayanan, N. S. (2015). Medial frontal~ 4-Hz activity in humans and rodents is attenuated in PD patients and in rodents with cortical dopamine depletion. *Journal of neurophysiology*, *114*(2), 1310-1320.

Pavlides, A., Hogan, S. J., & Bogacz, R. (2015). Computational models describing possible mechanisms for generation of excessive beta oscillations in Parkinson's disease. PLoS computational biology, 11(12), e1004609.

Pavone, E. F., Marzi, C. A., & Girelli, M. (2009). Does subliminal visual perception have an error-monitoring system?. European Journal of Neuroscience, 30(7), 1424-1431.

Pavone EF, Tieri G, Rizza G, Tidoni E, Grisoni L, Aglioti SM. (2016) Embodying others in immersive virtual reality: electro-cortical signatures of monitoring the errors in the actions of an avatar seen from a first-person perspective. J Neurosci 36: 268–279.

Pazzaglia, M., Smania, N., Corato, E., & Aglioti, S. M. (2008). Neural underpinnings of gesture discrimination in patients with limb apraxia. Journal of Neuroscience, 28(12), 3030-3041.

Pernigo, S., Moro, V., Avesani, R., Miatello, C., Urgesi, C., & Aglioti, S. M. (2012). Massive somatic deafferentation and motor deefferentation of the lower part of the body impair its visual

recognition: A psychophysical study of patients with spinal cord injury. European Journal of Neuroscience, 36(11), 3509–3518.

Perrin F, Pernier J, Bertrand O, Echallier JF. (1989) Spherical splines for scalp potential and current density mapping. Electroencephalogr Clin Neurophysiol 72: 184–187.

Pezzulo G, Cisek P. Navigating the affordance landscape: feedback control as a process model of behavior and cognition. Trends Cogn Sci 20: 414–424, 2016. doi:10.1016/j.tics.2016.03.013.

Pfurtscheller G, Lopes da Silva FH. (1999) Event-related EEG/MEG synchronization and desynchronization: basic principles. Clin Neurophysiol 110: 1842– 1857.

Pfurtscheller, G., Neuper, C., Brunner, C., & Da Silva, F. L. (2005). Beta rebound after different types of motor imagery in man. *Neuroscience letters*, *378*(3), 156-159.

Phillips, J. M., Vinck, M., Everling, S., & Womelsdorf, T. (2013). A long-range fronto-parietal 5-to 10-Hz network predicts "top-down" controlled guidance in a task-switch paradigm. Cerebral Cortex, 24(8), 1996-2008.

Polich, J. (2007). Updating P300: an integrative theory of P3a and P3b. Clinical neurophysiology, 118(10), 2128-2148.

Porcaro, C., Balsters, J. H., Mantini, D., Robertson, I. H., & Wenderoth, N. (2019). P3b amplitude as a signature of cognitive decline in the older population: An EEG study enhanced by Functional Source Separation. NeuroImage, 184, 535-546.

Proverbio, A. M., Crotti, N., Manfredi, M., Adorni, R., & Zani, A. (2012). Who needs a referee? How incorrect basketball actions are automatically detected by basketball players' brain. Scientific Reports, 2.

R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing, 2014. https:// www.R-project.org/.

Raven, J. C. Court JH, Raven J (1988) Manual for Raven's progressive matrices and vocabulary

Ridderinkhof KR, Ramautar JR, Wijnen JG. (2009) To PE or not to PE: a P3-like ERP component reflecting the processing of response errors. Psychophysiology 46: 531–538.

Ridderinkhof KR, Ullsperger M, Crone EA, Nieuwenhuis S. (2004) The role of the medial frontal cortex in cognitive control. Science 306: 443–447.

Ridderinkhof, K. R. (2014). Neurocognitive mechanisms of perception–action coordination: A review and theoretical integration. Neuroscience & Biobehavioral Reviews, 46, 3-29.

Ridderinkhof, K. R., & Brass, M. (2015). How kinesthetic motor imagery works: A predictive-processing theory of visualization in sports and motor expertise. Journal of Physiology Paris, 109(1–3), 53–63.

Ridderinkhof, K. R., Ramautar, J. R., & Wijnen, J. G. (2009). To PE or not to PE: A P3-like ERP component reflecting the processing of response errors. Psychophysiology, 46(3), 531-538.

Ridderinkhof, K. R., Van Den Wildenberg, W. P., Segalowitz, S. J., & Carter, C. S. (2004). Neurocognitive mechanisms of cognitive control: the role of prefrontal cortex in action selection, response inhibition, performance monitoring, and reward-based learning. Brain and cognition, 56(2), 129-140.

Rietveld, E. (2012). Bodily intentionality and social affordances in context. Consciousness in interaction. The role of the natural and social context in shaping consciousness, 207-226.

Rorden, C., Brett, M. (2000). Stereotaxic display of brain lesions. Behavioural Neurology. 12, 191-200.

Rothi, L. J., Heilman, K. M., & Watson, R. T. (1985). Pantomime comprehension and ideomotor apraxia. Journal of Neurology, Neurosurgery & Psychiatry, 48(3), 207-210.

Rowe Dr., R., Horswill, M. S., Kronvall-Parkinson, M., Poulter, D. R., & McKenna, F. P. (2009). The effect of disguise on novice and expert Tennis players' anticipation ability. Journal of Applied Sport Psychology, 21(2), 178–185.

Sanchez-Vives, M. V., & Slater, M. (2005). From presence to consciousness through virtual reality. Nature Reviews Neuroscience, 6(4), 332.

Sauseng P, Klimesch W, Doppelmayr M, Pecherstorfer T, Freunberger R, Hanslmayr S. (2005) EEG alpha synchronization and functional coupling during top-down processing in a working memory task. Hum Brain Mapp 26:148–155.

Sauseng P, Klimesch W, Gruber WR, Hanslmayr S, Freunberger R, Doppelmayr M. Are event-related potential components generated by phase resetting of brain oscillations? A critical discussion. Neuroscience 146: 1435–1444, 2007.

Sauseng, P., & Klimesch, W. (2008). What does phase information of oscillatory brain activity tell us about cognitive processes? Neuroscience & Biobehavioral Reviews, 32(5), 1001-1013.

Schwartz AB, Moran DW, Reina GA. (2004) Differential representation of perception and action in the frontal cortex. Science 303: 380–383.

Sebanz, N., & Shiffrar, M. (2009). Detecting deception in a bluffing body: The role of expertise. Psychonomic Bulletin and Review, 16(1), 170–175.

Seer, C., Lange, F., Georgiev, D., Jahanshahi, M., & Kopp, B. (2016). Event-related potentials and cognition in Parkinson's disease: an integrative review. *Neuroscience & Biobehavioral Reviews, 71,* 691-714.

Seer, C., Lange, F., Loens, S., Wegner, F., Schrader, C., Dressler, D., ... & Kopp, B. (2017). Dopaminergic modulation of performance monitoring in Parkinson's disease: An event-related potential study. Scientific reports, 7, 41222.

Senna, I., Bolognini, N., & Maravita, A. (2014). Grasping with the foot: Goal and motor expertise in action observation. Human Brain Mapping, 35(4), 1750–1760.

Shalgi S, Barkan I, Deouell LY. (2009) On the positive side of error processing: error-awareness positivity revisited. Eur J Neurosci 29: 1522–1532.

Singh, A., Richardson, S. P., Narayanan, N., & Cavanagh, J. F. (2018). Mid-frontal theta activity is diminished during cognitive control in Parkinson's disease. *Neuropsychologia*.

Sirigu, A., Daprati, E., Pradat-Diehl, P., Franck, N., & Jeannerod, M. (1999). Perception of self-generated movement following left parietal lesion. Brain, 122(10), 1867-1874.

Sirigu, A., Duhamel, J. R., Cohen, L., Pillon, B., Dubois, B., & Agid, Y. (1996). The mental representation of hand movements after parietal cortex damage. Science, 273(5281), 1564-1568.

Slater, M., Pérez Marcos, D., Ehrsson, H., & Sanchez-Vives, M. V. (2008). Towards a digital body: the virtual arm illusion. Frontiers in human neuroscience, 2, 6.

Slater M, Spanlang B, Sanchez-Vives MV, Blanke O. (2010) First person experience of body transfer in virtual reality. PLoS One 5: e10564.

Slobounov SM, Ray W, Johnson B, Slobounov E, Newell KM. (2015) Modulation of cortical activity in 2D versus 3D virtual reality environments:an EEG study. Int J Psychophysiol 95: 254–260.

Spinelli G, Tieri G, Pavone EF, Aglioti SM. (2018) Wronger than wrong: Graded mapping of the errors of an avatar in the performance monitoring system of the onlooker. Neuroimage 167: 1–10.

Spinnler, H., & Tognoni, G. (1987). Italian Group on the Neuropsychological Study of Ageing: Italian standardization and classification of neuropsychological tests. Ital J Neurol Sci, 6(8), 1-120.

Stapel, J. C., Hunnius, S., van Elk, M., & Bekkering, H. (2010). Motor activation during observation of unusual versus ordinary actions in infancy. *Social Neuroscience*, *5*(5-6), 451-460.

Steinhauser, M., & Yeung, N. (2010). Decision processes in human performance monitoring. Journal of Neuroscience, 30(46), 15643-15653.

Steinhauser, R., Maier, M. E., & Steinhauser, M. (2017). Neural signatures of adaptive post-error adjustments in visual search. *Neuroimage*, *150*, 270-278.

Stout, D. (2010). The evolution of cognitive control. Topics in Cognitive Science, 2(4), 614-630.

Swick, D., & Turken, U. (2002). Dissociation between conflict detection and error monitoring in the human anterior cingulate cortex. Proceedings of the National Academy of Sciences, 99(25), 16354-16359.

Tadel F, Baillet S, Mosher JC, Pantazis D, Leahy RM. (2011) Brainstorm: a user-friendly application for MEG/EEG analysis. Comput Intell Neurosci 2011: 879716.

Talairach, J., & Tournoux, P. (1988). Co-Planar Stereotaxic Atlas of the Human Brain: 3-D Proportional System: An Approach to Cerebral Imaging (Thieme Classics). Thieme.

Tan, Y., Vandeput, J., Qiu, J., Van den Bergh, O., & von Leupoldt, A. (2019). The error-related negativity for error processing in interoception. NeuroImage, 184, 386-395.

Tecchia F, Avveduto G, Brondi R, Carrozzino M, Bergamasco M, Alem L. I'm in VR! In: Proceedings of the 20th ACM Symposium on Virtual Reality Software and Technology-VRST'14. New York: Association for Computing Machinery, 2014, p. 73–76.

Tecchia, F., Carrozzino, M., Bacinelli, S., Rossi, F., Vercelli, D., Marino, G., ... & Bergamasco, M. (2010). A flexible framework for wide-spectrum VR development. Presence: Teleoperators and Virtual Environments, 19(4), 302-312.

Tieri, G., Morone, G., Paolucci, S., & Iosa, M. (2018). Virtual reality in cognitive and motor rehabilitation: facts, fiction and fallacies. Expert review of medical devices, 15(2), 107-117.

Tieri G, Tidoni E, Pavone EF, Aglioti SM (2015a). Body visual discontinuity affects feeling of ownership and skin conductance responses. Sci Rep 5: 17139.

Tieri G, Tidoni E, Pavone EF, Aglioti SM (2015b). Mere observation of body discontinuity affects perceived ownership and vicarious agency over a virtual hand. Exp Brain Res 233: 1247–1259.

Tomasino, B., Guatto, E., Rumiati, R. I., & Fabbro, F. (2012). The role of volleyball expertise in motor simulation. Acta Psychologica, 139(1), 1–6.

Trujillo LT, Allen JJ. (2007) Theta EEG dynamics of the error-related negativity. Clin Neurophysiol 118: 645–668.

Trujillo, L. T., & Allen, J. J. (2007). Theta EEG dynamics of the error-related negativity. Clinical Neurophysiology, 118(3), 645-668.

Tsujimoto T, Shimazu H, Isomura Y. (2006) Direct recording of theta oscillations in primate prefrontal and anterior cingulate cortices. J Neurophysiol 95:2987–3000.

Turchet, L. (2015). Designing presence for real locomotion in immersive virtual environments: an affordance-based experiential approach. Virtual Reality, 19(3-4), 277-290.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., ... & Joliot, M. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage, 15(1), 273-289.

Tzur G, Berger A. (2007) When things look wrong: theta activity in rule violation. Neuropsychologia 45: 3122–3126.

Ullsperger M, Danielmeier C, Jocham G. (2014) Neurophysiology of performance monitoring and adaptive behavior. Physiol Rev 94: 35–79.

Ullsperger M, Falkenstein M. Leipzig, Germany: Max Planck Institute for Cognitive Neuroscience, 2004, p. 124–129.

Ullsperger, M., & von Cramon, D. Y. (2006). The role of intact frontostriatal circuits in error processing. *Journal of Cognitive Neuroscience*, *18*(4), 651-664.

Ullsperger, M., Fischer, A. G., Nigbur, R., & Endrass, T. (2014). Neural mechanisms and temporal dynamics of performance monitoring. Trends in Cognitive Sciences, 18(5), 259-267.

Urgesi, C., Moro, V., Candidi, M., & Aglioti, S. M. (2006). Mapping Implied Body Actions in the Human Motor System. Journal of Neuroscience, 26(30), 7942–7949.

Vallesi, A., McIntosh, A. R., & Stuss, D. T. (2011). Overrecruitment in the aging brain as a function of task demands: evidence for a compensatory view. Journal of Cognitive Neuroscience, 23(4), 801-815.

Vallesi, A., Stuss, D. T., McIntosh, A. R., & Picton, T. W. (2009). Age-related differences in processing irrelevant information: evidence from event-related potentials. Neuropsychologia, 47(2), 577-586.

Van Boxtel, G. J., Van Der Molen, M. W., & Jennings, J. R. (2005). Differential involvement of the anterior cingulate cortex in performance monitoring during a stop-signal task. Journal of Psychophysiology, 19(1), 1.

van Driel J, Ridderinkhof KR, Cohen MX. (2012) Not all errors are alike: theta and alpha EEG dynamics relate to differences in error-processing dynamics. J Neurosci 32: 16795–16806.

van Gaal, S., Ridderinkhof, K. R., Fahrenfort, J. J., Scholte, H. S., & Lamme, V. A. (2008). Frontal cortex mediates unconsciously triggered inhibitory control. Journal of Neuroscience, 28(32), 8053-8062.

van Pelt S, Heil L, Kwisthout J, Ondobaka S, van Rooij I, Bekkering H. (2016) Beta- and gamma-band activity reflect predictive coding in the processing of causal events. Soc Cogn Affect Neurosci 11: 973–980.

van Schie HT, Mars RB, Coles MG, Bekkering H. (2004) Modulation of activity in medial frontal and motor cortices during error observation. Nat Neurosci 7: 549–554.

van Schie, H. T., Koelewijn, T., Jensen, O., Oostenveld, R., Maris, E., & Bekkering, H. (2008). Evidence for fast, low-level motor resonance to action observation: an MEG study. *Social Neuroscience*, *3*(3-4), 213-228.

Vanbellingen, T., Kersten, B., Van Hemelrijk, B., Van de Winckel, A., Bertschi, M., Müri, R., ... & Bohlhalter, S. (2010). Comprehensive assessment of gesture production: a new test of upper limb apraxia (TULIA). European journal of neurology, 17(1), 59-66

Vecchiato, G., Del Vecchio, M., Ascari, L., Antopolskiy, S., Deon, F., Kubin, L., ... & Avanzini, P. (2018). Electroencephalographic time-frequency patterns of braking and acceleration movement preparation in car driving simulation. Brain research.

Vecchiato G, Tieri G, Jelic A, De Matteis F, Maglione AG, Babiloni F. (2015) Electroencephalographic correlates of sensorimotor integration and embodiment during the appreciation of virtual architectural environments. Front Psychol 6: 1944.

Verleger, R., Schroll, H., & Hamker, F. H. (2013). The unstable bridge from stimulus processing to correct responding in Parkinson's disease. *Neuropsychologia*, *51*(13), 2512-2525.

Villa R, Tidoni E, Porciello G, Aglioti SM. (2018) Violation of expectations about movement and goal achievement leads to sense of agency reduction. Exp Brain Res 236: 2123–2135.

Völker, M., Fiederer, L. D., Berberich, S., Hammer, J., Behncke, J., Kršek, P., ... & Helias, M. (2018). The dynamics of error processing in the human brain as reflected by high-gamma activity in noninvasive and intracranial EEG. NeuroImage, 173, 564-579.

Voloh, B., Valiante, T. A., Everling, S., & Womelsdorf, T. (2015). Theta–gamma coordination between anterior cingulate and prefrontal cortex indexes correct attention shifts. Proceedings of the National Academy of Sciences, 112(27), 8457-8462.

Volpato C, Schiff S, Facchini S, Silvoni S, Cavinato M, Piccione F, Antonini A, Birbaumer N. (2016) Dopaminergic medication modulates learning from feedback and error-related negativity in Parkinson's disease: a pilot study. Front Behav Neurosci 10: 205.

Wang L, Tang D, Zhao Y, Hitchman G, Wu S, Tan J, Chen A. (2015) Disentangling the impacts of outcome valence and outcome frequency on the post-error slowing. Sci Rep 5: 8708.

Wang, & Tu. (2017). Neural Correlates of Expert Behavior During a Domain-Specific Attentional Cueing Task in Badminton Players. Journal of Sport and Exercise Psychology, 39(3), 209–221.

Wang, C.-H. H., Yang, C. T., Moreau, D., Muggleton, N. G., & Tu, K.-C. (2017). Motor expertise modulates neural oscillations and temporal dynamics of cognitive control. Journal of Sport and Exercise Psychology, 39(1), 209–221.

Weast, J. A., Walton, A., Chandler, B. C., Shockley, K., & Riley, M. A. (2014). Essential kinematic

information, athletic experience, and affordance perception for others. Psychonomic Bulletin and Review, 21(3), 823–829.

Wessel JR, Danielmeier C, Ullsperger M. (2011) Error awareness revisited: accumulation of multimodal evidence from central and autonomic nervous systems. J Cogn Neurosci 23: 3021–3036.

Wessel JR, Klein TA, Ott DV, Ullsperger M. (2014) Lesions to the prefrontal performance-monitoring network disrupt neural processing and adaptive behaviors after both errors and novelty. Cortex 50: 45–54.

Wessel JR. (2012) Error awareness and the error-related negativity: evaluating the first decade of evidence. Front Hum Neurosci 6: 88.

Willemssen, R., Müller, T., Schwarz, M., Hohnsbein, J., & Falkenstein, M. (2008). Error processing in patients with Parkinson's disease: the influence of medication state. *Journal of neural transmission*, *115*(3), 461-468.

Wilson, B., Cockburn, J., & Halligan, P. (1987). Development of a behavioral test of visuospatial neglect. Archives of physical medicine and rehabilitation, 68(2), 98-102.

Wokke ME, Cleeremans A, Ridderinkhof KR. (2017) Sure I'm sure: prefrontal oscillations support metacognitive monitoring of decision making. J Neurosci 37: 781–789.

Wokke, M. E., Knot, S. L., Fouad, A., & Ridderinkhof, K. R. (2016). Conflict in the kitchen: Contextual modulation of responsiveness to affordances. Consciousness and cognition, 40, 141-146

Woodman, G. F. (2010). Masked targets trigger event-related potentials indexing shifts of attention but not error detection. *Psychophysiology*, *47*(3), 410-414.

Wu Y, Zhou X. (2009) The P300 and reward valence, magnitude, and expectancy in outcome evaluation. Brain Res 1286: 114–122.

Wu, Y., Zeng, Y., Zhang, L., Wang, S., Wang, D., Tan, X., … Zhang, J. (2013). The role of visual perception in action anticipation in basketball athletes. Neuroscience, 237, 29–41.

Yang, J., Andric, M., & Mathew, M. M. (2015). The neural basis of hand gesture comprehension: a meta-analysis of functional magnetic resonance imaging studies. Neuroscience & Biobehavioral Reviews, 57, 88-104.

Yazmir B, Reiner M. (2016) Neural correlates of user-initiated motor success and failure—A brain-computer interface perspective. Neuroscience S0306-4522(16)30600-5.

Yeung N, Bogacz R, Holroyd CB, Nieuwenhuis S, Cohen JD. (2007) Theta phase resetting and the error-related negativity. Psychophysiology 44: 39–49.

Yeung, N., Botvinick, M. M., & Cohen, J. D. (2004). The neural basis of error detection: conflict monitoring and the error-related negativity. Psychological review, 111(4), 931.

Yordanova J, Kolev V, Kirov R. (2012) Brain oscillations and predictive processing. Front Psychol 3: 416.

Overview of publications related to the PhD Program

- **Pezzetta, R.**, Nicolardi, V., Tidoni, E., & Aglioti, S. M. (2018). Error, rather than its probability, elicits specific electrocortical signatures: a combined EEG-immersive virtual reality study of action observation. *Journal of neurophysiology*. https://doi.org/10.1152/jn.00130.2018 **(Chapter 3)**

- Ozkan, D.*, **Pezzetta, R.*** (2017) Predictive monitoring of actions, EEG recordings in virtual reality. *Journal of Neurophysiology*, 119(4), 1254-1256. *equal contribution https://doi.org/10.1152/jn.00825.2017 **(Chapter 2)**

- Spinelli, G., Canzano L., **Pezzetta, R**., Tidoni, E., & Aglioti, S. M. (*in preparation*). Altered EEG dynamics of action monitoring in Ideomotor Apraxia. **(Chapter 4)**

- **Pezzetta, R.**, Okzan, D., Tieri, G., Era, V., Zabberoni, S., Peppe, A., Costa, A., Carlesimo, A., Caltagirone, C., & Aglioti, S.M. (*in preparation*). Embodying action errors in virtual reality: EEG data on Parkinson's Disease. **(Chapter 5)**

- Ozkan, D., **Pezzetta, R.**, Moreau, Q., Abreu, A., & Aglioti, S.M. (*in preparation*). Predicting the fate of basketball throws: an EEG study in Wheelchair Basketball players **(Chapter 7)**

- Casula, E., Tieri, G., Maiella, M., **Pezzetta, R.**, Pavone, E., Aglioti, SMA., Koch, G. (*in preparation*). Real-time assessment of brain dynamics during embodiment: a TMS-EEG-IVR study.

Overview of publications not related to the PhD Program

- **Pezzetta R.***, Crescentini, C.*, Urgesi C., Fabbro, F., (2015) review "Contributions of neuroscience to the study of meditation and spirituality", GIORNALE ITALIANO DI PSICOLOGIA, vol 42, ISSN: 0390-5349, doi: 10.1421/81939. *equal contribution

- Arcara G., **Pezzetta R.**, Rizzi G., Formica F., Benavides-Varela S., Turco C., Piccione F. Semenza C. "How and where is simple multiplication is solved? The interaction of the two hemispheres revealed by MEG" (*under revision in Neuroimage*)

Overview of Publication Status of Chapters in Thesis

You are kindly requested to indicate which of the thesis chapters are original, have been submitted for publication, or have been accepted/published by filling out the first column (chapter number and title) and tick the appropriate box columns:

Chapter number and title	**Original text (not published before)**	**Accepted/ published**
Chapter 1. Introduction	X	
Chapter 2. Predictive monitoring of actions, EEG recordings in virtual reality		X Journal of Neurophysiology (2017)
Chapter 3. Error, rather than its probability, elicits specific electrocortical signatures: a combined EEG immersive virtual reality study of action observation		X Journal of Neurophysiology (2018)
Supplementary material of Chapter 3	X	
Chapter 4. Altered EEG dynamics of action and error monitoring in Ideomotor Apraxia	X	
Supplementary material of Chapter 4	X	
Chapter 5. Error monitoring in Parkinson's Disease: preliminary EEG data	X	
Supplementary material of Chapter 5	X	
Chapter 6. General Discussion	X	
Appendix Chapter 7. Predicting the fate of basketball throws: an EEG study in Wheelchair Basketball players	X	

Acknowledgments

An acknowledgment goes to the people that has been part of this story during the last 3 years. It is impossible to list all the persons from whom I received scientific knowledge and personal support, but I will always be grateful. Doing science is probably the most exciting job to do, but surely it rises obstacles and frustrations along the way. Having the right people on your side, just place everything in a different perspective!

First, I would like to thank my PhD supervisor, Professor Aglioti, for introducing me to this fascinating world of *errors and theta*, for his passion and for having motivated and forced me to always try to go one step further. I will always be grateful for the human support during the more personal moments that had occurred during this period of life.

Gratitude to the external reviewers who accepted do read this thesis. Thanks for your valuable time.

Credits to Michela, our Lab Manager for all the times she helped beyond her duties.

A special thanks to my friends in the AgliotiLab and in Santa Lucia, which happen to be also colleagues. At the end, they have been the persons with whom I spent most of my hours and emotions of the last years! I cannot list all the persons I shared project, ideas, frustration, discussions, nights, laugh and food with, but it wouldn't be the same without them all (and much less fun!). I will never forget the 'Daje Rachele' created with their body figures, it was the moment in which I understood that they are not only a Lab, but my messy Roman Family.

A thought to Enea Francesco Pavone, who started this research line with his paper in the 2016.

A warm *dank je wel* to Richard, for our meetings in front of the ginger tea, discussing from the most fascinating aspects of neuroscience to bird migration, and decision making of chicken-sex! Thanks to him and his team (at the UvA and trans-oceanic), for all the time spent examining ideas and building the experiment together, brick by brick.

Always gratitude to my family, my aunt, my oldest friends in Friuli, Padova and around the world…for their support, their inopportune jokes and for making me feel home, everywhere I am.

A final thought to Giorgio, for being the best life companion one can wishes for.