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Frontal electrophysiological markers of performance monitoring and exploratory behaviour in humans

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**Frontal electrophysiological
markers of performance monitoring
and exploratory behaviour in
humans**

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ABSTRACT

The survival of every living being is strongly relying on its ability to detect changes in the environment and on its speed to adapt efficiently. Within this context, cognitive functions that support exploration to find solutions and verification to reduce uncertainty and increase the efficiency of our actions are very relevant to behavioral adaptation.

It has been shown that the prefrontal cortex plays a leading role in the executive control and regulation of these functions, especially the lateral prefrontal cortex (LPFC) and the medial cingulate cortex (MCC), although the processes that underlie them still pose challenges for their total understanding. Understanding the neuronal mechanisms and dynamics that carry out the evaluation of performance could also be the basis to understand some of the alterations developing in neurodegenerative pathologies such as Parkinson's disease (PD) and in behavioral disorders such as obsessive-compulsive disorder.

This thesis seeks to evaluate the functions support adaptive behavior by adapting experimental protocols designed for studies of non-human primates to carry out studies in humans by means of electroencephalography techniques, and identify markers of adaptive functions. In a first study, feedback-related negativity (FRN) was evaluated, which has been shown to have a relationship with learning and the dopamine system, and oscillations evoked by feedback in a problem-solving task by trial and error. The study challenged exploratory behavior and exploitation in control subjects and in patients with Parkinson's disease, and demonstrated the sensitivity of these markers to the subject group, especially the sensitivity of beta activity related to monitoring performance. The second study addressed information search processes that reduce uncertainty, through a protocol applied in young and healthy human subjects. The experimental task challenged the verification process using positive and negative reinforcements and visual information on trends in performance. The study evidenced behavioral strategies and the underlying neural dynamics in frontal regions that contribute to decision-making during information seeking and verification.

KEYWORDS

Exploration, Verification, Uncertainty, Prefrontal Cortex, EEG

RESUME FRANCAIS

La survie de chaque être vivant repose fortement sur sa capacité à détecter les changements dans l'environnement et sur sa rapidité à s'adapter efficacement. Dans ce contexte, les fonctions cognitives qui soutiennent l'exploration - pour trouver des solutions aux problèmes- et la vérification - pour réduire l'incertitude et augmenter l'efficacité de nos actions- sont très pertinentes pour l'adaptation comportementale.

Il a été démontré que le cortex préfrontal joue un rôle de premier plan dans le contrôle exécutif et la régulation de ces fonctions, en particulier le cortex préfrontal latéral (LPFC) et le cortex cingulaire médial (MCC), bien que les processus qui sous-tendent ces processus cognitifs posent encore des défis pour les neurosciences. Comprendre les mécanismes et les dynamiques neuronales qui effectuent l'évaluation des performances pourrait également être la base pour comprendre certaines des altérations qui se développent dans les pathologies neurodégénératives telles que la maladie de Parkinson (MP) et dans les troubles du comportement tels que le trouble obsessionnel-compulsif.

Cette thèse vise à évaluer les fonctions supportant le comportement adaptatif en adaptant des protocoles expérimentaux destinés aux études de primates non humains pour réaliser des études chez l'humain au moyen de techniques d'électroencéphalographie, et à identifier des marqueurs de fonctions adaptatives. Dans une première étude, la négativité liée au feedback (FRN) de performance, dont le rôle dans l'apprentissage et la relation avec le système dopaminergique ont été proposés, a été évaluée, ainsi que les oscillations évoquées par le feedback de performance dans une tâche de résolution de problèmes par essais et erreurs. L'étude a concerné le comportement exploratoire et l'exploitation chez des sujets témoins et chez des patients atteints de la maladie de Parkinson, et a démontré la sensibilité de marqueurs, en particulier la sensibilité de l'activité bêta liée au suivi des performances et à la condition des sujets. La deuxième étude portait sur les processus de recherche d'information, grâce à un protocole appliqué à des sujets humains jeunes et en bonne santé. La tâche expérimentale utilisée provoquait des décisions de vérification en utilisant des renforcements positifs et négatifs et des indices visuels sur l'évolution des performances. L'étude a mis en évidence des stratégies comportementales et les dynamiques neuronales sous-jacentes dans les régions frontales qui contribuent à la prise de décision lors de la recherche et de la vérification d'information

"The presence of those seeking the truth is infinitely to be preferred to the presence of those who think they've found it"

Terry Pratchett

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1. Executive Functions and Adaptation

“It is a law of nature we overlook, that intellectual versatility is the compensation for change, danger, and trouble. An animal perfectly in harmony with its environment is a perfect mechanism. Nature never appeals to intelligence until habit and instinct are useless. There is no intelligence where there is no change and no need of change. Only those animals partake of intelligence that have a huge variety of needs and dangers.” H.G. Wells. *The Time Machine*

In “*The Time Machine*,” the iconic science fiction story, when the Traveler reaches the year 802,701, he finds that the human race as we know it no longer exists. In its place are harmless, tender, carefree, and unintelligent beings. On the basis of what he sees, he concludes that the domination of nature and the comfortable stance toward the environment has eliminated the need for intelligence in those beings, establishing a relationship based on how intelligence is a need that imposes a problematic and challenging environment to the beings that live there. Luckily, for us, our environment only increases its dynamism, its technological changes, information flow, and social requirements, among many other factors, forcing us to be flexible and to adapt our behavior with the vital capacity to change our strategies based on constant environmental changes.

The ability to react to errors, adapt our decisions, and plan our actions in order to achieve a goal is an essential aspect of human survival. This ability to adapt behavior based on changes in the environment has been attributed to a particular set of cognitive processes, called executive functions. Executive functions are defined as a set of higher cognitive functions that regulate sensory, motor, cognitive, memory, and affective capacities (Chamberlain et al., 2005). Therefore, executive functioning can be defined as the opposite of routine functioning. In fact, every time our repertoire of learned skills, habits, and reflexes is not sufficient to manage a situation, executive functions are likely to intervene.

Executive functions are necessary in order to carry out new or complex tasks that require establishing an objective, planning, and choosing different sequences of behavior that will lead to achieving the said objective. These action plans are compared on the basis of the possibility of succeeding, implementing the chosen plan, and finally, making corrections in the event of failure. Different theoretical models suggest that executive functions enable superior behavioral control to be established, which is implemented when routine actions need to be modified or reorganized (Dehaene & Changeux, 1997; Tim Shallice, 1988).

In routine situations, our actions (associations established through learning, such as habits) are based on processes of rapid, automatic selection. However, a particular instruction or unexpected event can trigger “supervisory” control that overrides automatic processes.

Different processes can be distinguished among the components of executive functions, such as structured thinking, appropriately choosing a response, actively maintaining information (working memory) to plan and execute an action, avoiding ineffective behaviors, and memorizing tasks (Miller & Cohen, 2001; Walton et al., 2004).

In the 1970s, Luria (A. R. Luria, 1969), and later, Lezak (Muriel D. Lezak et al., 2004), attributed four components to executive functions:

- Volition or taking initiative: an intentional and complex process that allows a person to determine their needs, establish priorities, and act on them (M. D. Lezak, 1994), that is, forming an objective to be achieved.
- Planning: determining the actions necessary to achieve an objective and sequentially organizing these actions over time.
- Execution: implementing the prepared action plan.
- Self-monitoring: controlling the effectiveness of the actions in relation to the initial objective and ultimately correcting the action plan if necessary.

1.1. Role of rewards in behavioral adaptation

Implementing a behavior adapted to the context requires integrating sensory information flows and generating goal-oriented actions. This objective may be to obtain a reward. The concept of “reward” is an operational one that describes the positive value that an animal assigns to an object, an action, or an internal physical state and could be defined as an object or event that causes exploration and consumption behaviors and that enables one to learn these behaviors (Schultz, 2010).

In effect, certain objects or events in the environment serve as motivation, in part because of their importance for survival, reproduction, or personal well-being. This motivational or reward value, which varies depending on the organism’s state or needs, can be attributed to innate mechanisms (primary or unconditioned rewards, such as food) or through learning (secondary or conditioned rewards, such as money for human beings).

Goal-centered behavior requires constant exchanges between the search for strategies that provide pathways to rewards, called the exploration stage, and the use of this information to repeat successful results, exploitation. The exploitation stage implies repeating successful strategies until the environmental conditions or objectives change and return to the operating stage. To regulate this change in behavior, there is a control system that processes the information received and monitors and measures the performance of the actions taken, thus rapidly detecting and correcting errors and inappropriate behaviors (Bonini et al., 2014; Vidal et al., 2020). In addition to being used to correct errors, this monitoring system also works to guide strategy changes and, within its limits, to prevent future errors, thus ensuring efficient behavior and optimal performance (Kolling et al., 2012).

However, appropriately adapting to changes in the environment requires not only the presence of a reward as motivation for taking an action but also the ability to predict future rewards or punishments such as the presence of food or danger. It must also seek additional information that reduces uncertainty, decreases the action’s probability of

error, and increases its probability of success. In addition, curiosity and searching for information powerfully shape our behavior (Stoll, Fontanier, et al., 2016). An example of this is our social relationships. When deciding whether to trust a person, it is important to consider the information available. A greater amount of information increases the level of reliability, but our curiosity to search for information has to be regulated, and it has limits. An excess of questions or interest can be invasive and leave a negative impression of ourselves, which results in a social cost (Ma et al., 2020). In other applications, verification processes and additional information sampling can prevent us from leaving the house without keys or prevent our cell phone from running out of battery.

1.2. Executive functions and the prefrontal cortex

The importance of the frontal lobes in higher cognitive functions, such as reasoning, planning, and executive functions, began with the work of Harlow in the 1950s. In particular, the clinical case of patient Phineas Gage described by Dr. John Harlow marked a milestone in understanding the functionality of the frontal lobe (Harlow, 1999). In 1948, Gage suffered a prefrontal injury because of a work accident. After the accident, Gage experienced a dramatic change in behavior, characterized by a disregard for social conventions, difficulty in making decisions, and an inability to start or finish any project. This case represented the first relationship between prefrontal damage and altered behavior, initiating a series of studies on the role of the prefrontal cortex in normal executive functioning (Harlow, 1868). The description of the clinical consequences of a frontal lobe condition, particularly traumatic pathology (primarily due to war injuries) or tumors, has led to the identification of a long list of behavior changes (Barrash et al., 2018).

Starting in 1930, tests were developed, which evolved from a predominantly clinical approach to a psychometric approach toward executive dysfunctions. The study of patient populations also took the field beyond single case studies. The results of these

studies were not very encouraging in terms of specificity because of their reliance on relatively vague concepts of intelligence in keeping with the technical limitations of the time. With this method, specific behavior changes could not be correlated to a particular frontal injury (Chow, 2000; Goldstein, 1944; Smith, 1966). However, these studies did signify enormous progress in the study of cognitive functions among frontal patients, particularly by standardizing patient assessment procedures and collecting quantitative data.

In the second half of the 20th century, with the works of Luria (Alexandr Romanovich Luria, 1980) and Milner (Milner, 1982), the description of frontal syndromes was transformed owing to various improved specific neuropsychological tests to assess cognitive activity in the frontal lobe, such as behavioral flexibility and planning. These tests included *Wisconsin Card Sorting Test* (Grant & Berg, 1948), *Stroop Color Word Test* (Stroop, 1935), *Trail Making Test* (Reitan, 1958), Tower of London (Shallice et al., 1982), and a number of other assessments. In addition, these types of specific frontal functionality tests have made it possible to homogenize the concepts employed to describe the clinical views of patients with frontal dysfunctions.

Traditionally, as I described in the previous section, executive functions are attributed to frontal lobe functioning in general and prefrontal cortex structure functioning in particular. In addition, these cortical regions are richly supplied by the dopaminergic neurotransmitter system that plays an essential role in coordinating executive control (Procyk et al., 2000; S. M. Williams & Goldman-Rakic, 1993)(Williams, 1998; Procyk et al., 2016). Deficiencies in these networks can change decision-making and learning (Cavanagh & Frank, 2014; Maia & Frank, 2011)

Today, there is agreement that different areas of the prefrontal cortex play a fundamental role in this neural network. These cortical areas are highly interconnected and potentially highly interdependent. However, each region participates in different aspects of prefrontal functions (Lee et al., 2007; Rushworth et al., 2012). In addition, this region establishes important reciprocal connections with subcortical structures (diencephalon, midbrain), with the limbic system, with different associated sensory areas

(primarily somatic, auditory, and visual) (Robbins, 1990). This important intra- and extra-prefrontal innervation places the prefrontal cortex as the frontal lobe's association cortex.

The prefrontal cortex can traditionally be divided into three, with each part attributed to some functions in general:

- The lateral prefrontal cortex (LPFC) functionally controls different higher cognitive functions, particularly language, reasoning, and problem-solving; rule change processing in the course of an action (*set_shifting*); and working memory (Fuster, 2001; Goldman-Rakic, 1987; Procyk & Joseph, 1996; Watanabe et al., 2005).

- The orbitofrontal cortex (OFC), which comprises the base region of the frontal lobe, plays a role in the limbic functions that need frontal control, such as inhibition; encoding the motivational value of a stimulus, impulse control, interference, mood, and personality/social behavior (Bechara et al., 2000; E. T. Rolls, 2000).

- The medial prefrontal cortex (mPFC) is part of the cortical network that is responsible for cognitive control, particularly the Anterior Cingulate Cortex (ACC) and the Medial Cingulate Cortex (MCC). These have been involved in functions such as evaluating the results of an action, inhibition response, directing attention, conflict monitoring, and error detection (Amiez et al., 2013; Brown et al., 2020a; Hauser et al., 2017; Quilodran et al., 2008b).

1.3. Role of dopamine in reward processing and learning

Schultz's team (Wolfram Schultz, 1998) conducted electrophysiological studies in monkeys, which showed that a large number of dopaminergic neurons in the ventral tegmental area (VTA), and to a lesser extent, in the substantia nigra (SN), responded in a phasic manner. They presented low latency and short duration activity in response to a stimulus when the animal received food and/or juice in the course of exploratory movements, without being activated by the movement itself. In general, dopaminergic

neurons are activated phasically after receiving an unexpected primary reward (e.g., solid or liquid foods), either during learning in cognitive tests or outside any behavior test. This can be seen in the electrophysiological recording of a dopaminergic neuron of the VTA in monkeys in Figure 1.1. These neural responses do not vary by type of reward delivered to the animal.

Neural activity in response to rewards has also been recorded in structures targeted by dopaminergic projections. Numerous striatum interneurons respond to the distribution of an unanticipated primary reward (Apicella et al., 1997). Certain regions of the monkey's PFC also react to receiving primary rewards (Edmund T. Rolls, 2004; W. Schultz et al., 2000)

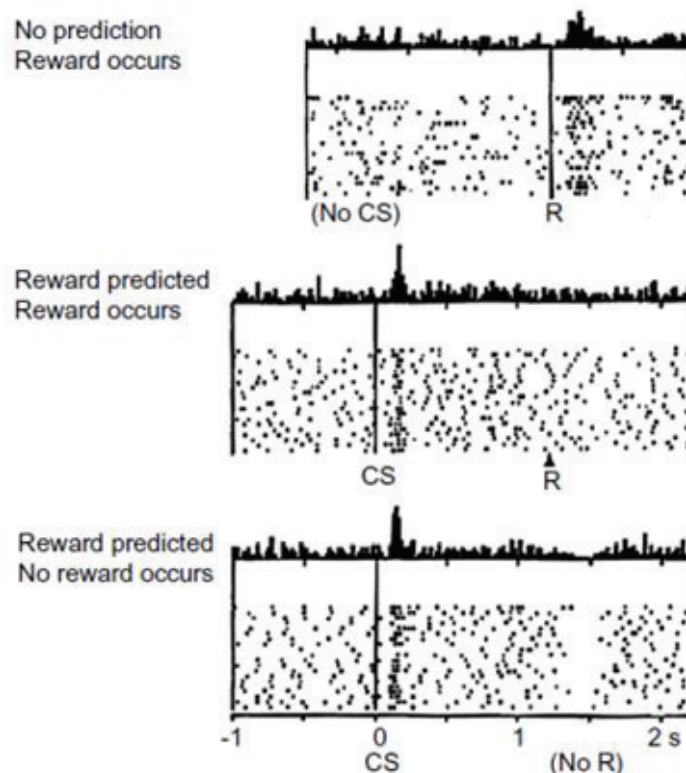


Fig. 1.1 Activity of a dopaminergic neuron in a nonhuman primate during an associative learning paradigm. (Top) Before learning, an unpredicted drop of fruit juice (R) is delivered (No CS = no reward-conditioned stimulus). (Middle) After learning (operational conditioning test that requires a simple motor response after presenting a conditioned stimulus), the conditioned stimulus (CS) predicts the

reward, and the reward matches the prediction. Now the dopaminergic neuron is activated by the reward-prediction stimulus and not by the reward itself. (Bottom) After learning, the conditioned stimulus predicts a reward, but the reward is not delivered because the animal makes an error in the test. The dopaminergic neuron activity decreases just at the moment when the reward was supposed to be given. At the same time, the dopaminergic neuron activity is aligned with reward delivery (top) or the appearance of the CS (middle and bottom). Each diagram shows the added neural activity, and the trial-by-trial activity (from top to bottom), of the same neuron, depending on time. Each dotted line corresponds to a trial, and the trials are indicated in their original order from top to bottom (Wolfram Schultz, 1998).

Data obtained from neuroimaging supports the idea of the participation from these regions, which are part of the corticostriatal circuits, in processing an unanticipated reward. Striatum and PFC activation varies after obtaining a primary reward (e.g., a pleasant tactile or taste sensation) (Francis et al., 1999; Small et al., 2001) or secondary reward (e.g., money) (Delgado et al., 2000; Elliott et al., 2000; Thut et al., 1997).

Rewards can act as an objective by successfully prompting searching, exploring, and consuming behavior. They can also stimulate learning, prompting the subject to repeat their behavior to obtain benefits (positive reinforcement) as clearly described by traditionally (or Pavlovian) or instrumental (or operant) conditioning procedures. They are also involved in maintaining learned behavior. Finally, it is well established that rewards induce positive emotions (which are, by nature, difficult to study in animals).

An associative learning situation, involving repeated and contingent pairing between an arbitrary stimulus and a primary reward, can prompt the animal toward exploration behavior that is comparable to that generated by the primary reward itself. These electrophysiological studies show that the activity of dopaminergic neurons, which participate in preparing the behavioral response, are transferred from the primary reward to the “conditioned” stimulus that precedes and therefore predicts it (Schultz, 1998), as described in Figure 2.1. This phenomenon has been considered from a motivational point

of view that is based on the cognitive psychology theory of learning by prompting (*incentive learning theory*), where a stimulus associated with a reward becomes an agent that reinforces behavior (Bindra, 1974; Dayan & Balleine, 2002).

2. Neurophysiological Markers of Executive Functions

The first electrophysiological recordings made in the ACC of monkeys revealed this region's role in detecting the action's results (Niki & Watanabe, 1976). Niki and Watanabe recorded the neural activity of mPFC in monkeys and observed that there was a group of neurons that responded each time a monkey made a mistake in a behavioral test.

In the early 1990s, owing to the use of electroencephalography (EEG), important advances were made in the study of ACC function linked to error and performance monitoring. An event-related potential (ERP) called error-related negativity (ERN) was described. ERN is presented in at least two forms. First, there is the “response ERN” that reflects the difference in neural processing between correct responses and incorrect responses in motor response tests. This ERN is a negative deflection of the ERP at the level of the frontal–central electrodes that can be seen around 100 ms after an incorrect answer (Falkenstein, Hoormann, et al., 2001; Gehring et al., 1992; Scheffers et al., 1996). Second, there is the “feedback ERN” (FRN) that reflects the difference in neural processing between incorrect and correct feedback in assumption tests and trial-and-error learning tests (Krigolson & Holroyd, 2007; Krigolson, 2018; Miltner et al., 1997). FRN is a negative ERP that occurs approximately 250 ms after negative feedback is presented (see Figure 2.1).

Functional magnetic resonance imaging and electroencephalography studies using signal source localization show that ERN/FRN is originally produced in the medial prefrontal cortex and more likely in the ACC (Amiez et al., 2012; Gehring & Willoughby, 2002; Kiehl et al., 2000; Nieuwenhuis et al., 2004; M. Ullsperger & von Cramon, 2001). According to the authors, both signals, ERN and FRN, reflect the same underlying physiological mechanism, a global function for detecting the error of mPFC, which would allow behavior to be adapted when the results of the action are negative. Because of the experimental work developed in nonhuman and human primates, new ideas have emerged on the role of the ACC in organizing behavior. These ideas are centered on the association between the action and its result and on assessing the costs/benefits of an action during decision-making (Rushworth et al., 2012; Rushworth & Behrens, 2008).

Different theoretical models suggest that monitoring actions and detecting errors do not depend exclusively on the ACC's functioning but rather on a system of brain structures that include the basal ganglia, the thalamus, and the activity of dopaminergic neurons (Falkenstein, Hoormann, et al., 2001; Clay B. Holroyd & Coles, 2002a). In this system, processing rewards, predicting them, and reinforcing learning plays a fundamental role in flexible behavior adaptation.

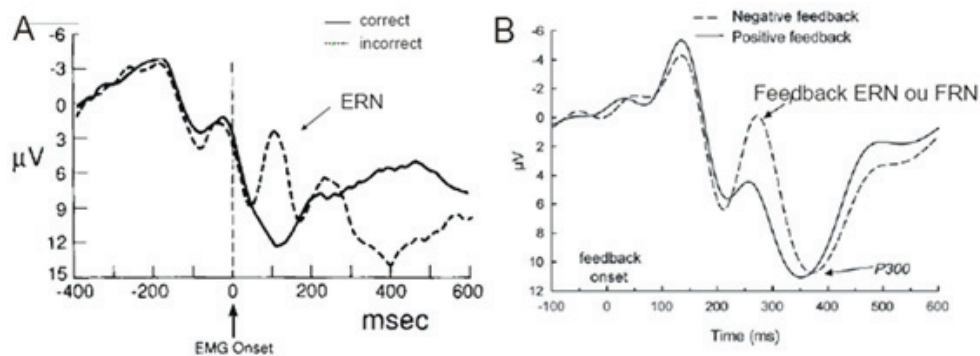


Fig. 2.1. Error-Related Negativity (ERN) and Feedback-Related Negativity (FRN) (Gehring et al., 1993; Nieuwenhuis et al., 2004). (A) On the left, the record of the ERN signal in a motor test is displayed, with time centered on the response's execution. (B) On the right, the record of the FRN signal is shown in response to a problem-solving test, with time centered on the appearance of the feedback. Both images show time in ms on the X-axis, while the magnitude of the EEG signal is quantified in μV on the Y-axis.

One evoked potential with characteristics similar to those of FRN is reward positivity (RewP), which has been reported in response to obtaining a reward. RewP presents a frontal–central location and is adjusted by dopamine's action, with a maximum range between 200 and 400 ms after the feedback, but with the difference of presenting a positive deflection (Brown et al., 2020a; Heydari & Holroyd, 2016; Proudfit et al., 2015). The difference could be subtle. The FRN would correspond to a potential for error in response to either negative feedback or a prediction error, while RewP would be formed by receiving a reward, including one obtained by surprise because of a better-than-expected result (Heydari & Holroyd, 2016).

Other ERPs that are associated with executive functions are:

- P3: this is a positive potential with a peak close to 300 ms post-stimulus and which may correspond to the most studied ERP component because of its relatively wide range and the ease of provoking it in experimental contexts (Kok, 2001; Polich, 2007). It is usually differentiated between P3a and P3b, depending on spatial distribution (Seer et al., 2016). Functional magnetic resonance imaging (fMRI) is used to indicate that P3b potential is related to the temporal–parietal junction and the medial temporal lobes and that P3a potential is attributed to the prefrontal cortex (Polich, 2007).

In tests that aim to evoke P3a potential, such as the Go/No-Go task, where participants are asked to respond to certain stimuli and refrain from responding to others (see Fig. 2.2), this potential seeks to reflect attention processes to detect either events that are irrelevant to the task (Escera & Corral, 2007) or alerts to surprising events (Barceló, 2003; Bruno Kopp & Lange, 2013).

- N2: this is a negative deflection potential that is seen at approximately 200 ms. It occurs during interference tasks, where the executive control performs conflict resolution (Seer et al., 2016). Experimental protocols such as the Simon Task (Simon & Rudell, 1967), where a conflict is created by having to read a word in an illogical context, for example, reading the word red, which is colored green, or the Flanker Task (Eriksen & Eriksen, 1974; B. Kopp et al., 1996; Willemsen et al., 2011), where one must respond on the basis of a stimulus flanked by logical ('> > > > >') or illogical distracting stimuli ('> > < > >') (see Fig. 2.2)

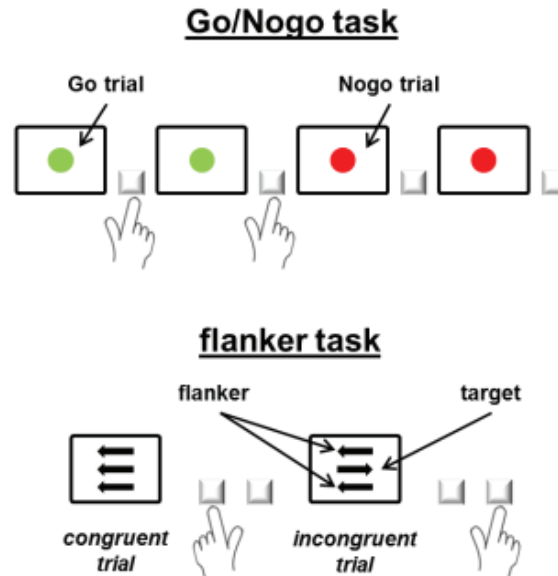


Fig. 2.2. Standard paradigms to record evoked potentials related to Executive Functions. (Top) Go/No-Go Task that requires participants to respond to certain stimuli (green circles, for example) and refrain from responding to others (red circles). (Bottom) In the Flanker Task, participants must respond on the basis of the stimulus information (direction of the center arrow) surrounded by distractors that may be logical or illogical, depending on the target information (Seer et al., 2016).

2.1. ACC and reinforcement learning theory

Holroyd and Coles proposed a theory that explained the reason for which ACC neurons are more active after incorrect responses in situations of conflict between several possible responses and after suppressing a reward (Clay B. Holroyd & Coles, 2002a). A priori, these three situations are apparently different, but they have one factor in common: the results of the actions are worse than expected. This constitutes an “error signal,” in the broad sense of the word, which activates the ACC, which, in turn, informs the executive system that it must change strategy in selecting future actions. This theory is founded on

the existence of, on the one hand, ERN and FRN, and on the other, dopaminergic projections toward the ACC, with the transmission of a prediction error, which would be the origin of this frontal signal connected to the error (Clay B. Holroyd & Coles, 2002a). In this model, a negative prediction error leads to the inhibition of dopaminergic neurons, which, in turn, disinhibits the ACC's neurons generated in the ERN and/or FRN.

The dopaminergic signal then allows the ACC to update the action's selection rules to optimize its performance or results. The MCC's role is to filter and decide upon the response that should be predicted to obtain the greatest reward. This theory explains the error responses to the negative feedback but does not consider that the MCC also evaluates positive feedback.

The interesting aspect of this theory is that it integrates dopamine's regulating action on the network of prefrontal regions in charge of executive control. It also allows us to electrophysiologically evaluate a cognitive process, such as detecting errors through the ERN/FRN signal. The dopaminergic neuron activity would facilitate the administration of cognitive resources by the medial prefrontal cortex when faced with new situations that necessitate learning. Therefore, the use of a problem-solving behavior test (trial and error) is an ideal tool for cognitive functioning such as evaluating an action's results.

There are different techniques to evaluate human cognitive processes. Traditionally, behavioral tests and neuropsychological tests have played an important role in cognitive evaluation. In the past few decades, the use of brain imaging techniques, such as functional magnetic resonance imaging (fMRI), proton emission tomography (PET), magnetoencephalography (MEG), and electroencephalography (EEG), has become common to study the neural bases of human cognition. In particular, EEG is a free, non-invasive tool with millisecond precision. All these characteristics make it an ideal technique to evaluate how cognitive processes adapt in healthy subjects and/or those with neurological diseases on an outpatient basis and with minimal discomfort for the participant.

2.2. MCC response in the exploratory process

To study the regulation of exploration/operating behavior on the basis of how different feedback is processed, Procyk & Goldman-Rakic(2006) designed the Problem-Solving Task (PST), which comprises two stages that alternate within the same problem (Fig. 2.3): an exploration period wherein the subject must search for the correct answer by trial and error (without receiving any indication from the researcher) and an exploitation period wherein the subjects must repeat the correct answer. At the end of each problem, a visual signal, called a change signal indicates (1) the end of the exploration period and (2) that a new problem has to be solved. Three important characteristics of the PST that serve to optimally evaluate the MCC's role in performance monitoring and to test the theory of reinforcement learning are as follows. First, all feedback that signals an error has an impact on the subject's decision in the following trial. Therefore, there is a clear connection between each problem's trials. Second, because the trial-and-error selection process eliminates possible solutions one by one as the test progresses, the probability of finding the correct answer, and therefore, expecting a positive result, increases during the exploration process. Third, the dissociation between the first correct answer during the search and correct answers during the repetition allows us to evaluate the MCC response to the positive feedback when they are unknown (exploration) and known to the subject (exploitation).

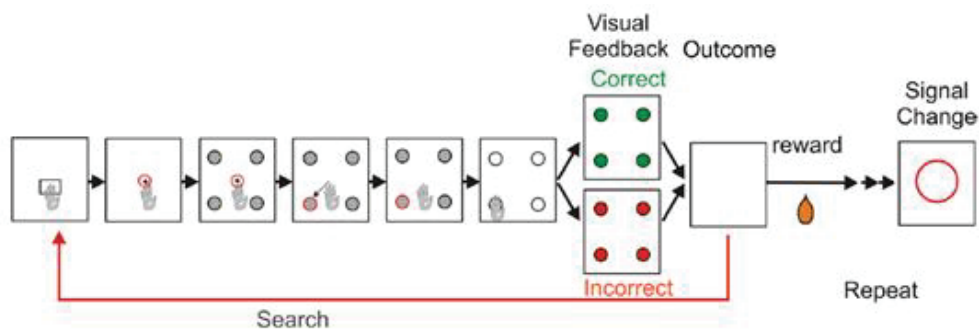


Fig. 2.3 *PST experimental protocol in monkey. The PST corresponds to a multiple-choice test with four options (targets), where the correct option must be found by trial and error. Giving the correct answer will deliver a reward (juice) and is represented by visual feedback in green (Exploration Stage). If the wrong option is chosen, feedback is provided in red. When the correct option is chosen for the first time in the problem, the task moves from exploration to exploitation because, now,*

the information obtained from previous choices must be used, and the same successful option must be repeated. At the end of each problem, a visual signal, called a change signal, indicates a new state of unknown response and the beginning of a new exploration stage (Vezoli & Procyk, 2009b).

The PST was developed as an experimental protocol in monkeys using a touch screen. The monkey must touch the center of the screen, which serves as a fixation point, and when the four options appear in a circle, the monkey must move its hand to one of the options. If the answer is incorrect, the color red is used, and if it is correct, the color green is used. The positive feedback image is associated with delivering positive reinforcement (reward) that comprises delivering a serving of juice to the monkey being assessed as an incentive for it to learn the test. Once the correct option is chosen, the monkey repeats the option to obtain the juice. After a variable series of repetitions (between 4 and 8 repetitions), a change signal appears, indicating the end of the problem and the beginning of a new search stage. The PST protocol's design ensures that participants not only focus on finding the correct answer but also monitor incorrect options in order to solve each problem without repeating the same errors.

Results for monkeys when the PST was conducted by Quilodran et al. (2008) show that the average MCC neuron activity evoked by negative feedback and the first instance of positive feedback for each problem is greater than that evoked by positive feedback in the repetition/exploitation stage (see Fig 2.4.). This reveals that some aspects of *feedback-related signals* are regulated by rules similar to those of reinforcement learning. Others seem to be more related to feedback categories and reflect the need to change behavioral strategies (Amiez et al., 2005; Khamassi et al., 2015; Quilodran et al., 2008b).

Another assumption is that performance control signals (FRN or ERN) follow the variation of dopaminergic signals or the state of dopaminergic transmission. This has been pharmacologically tested in nonhuman primates for FRN (Vezoli & Procyk, 2009b) and in humans (Patrick J. Zirnheld et al., 2004).

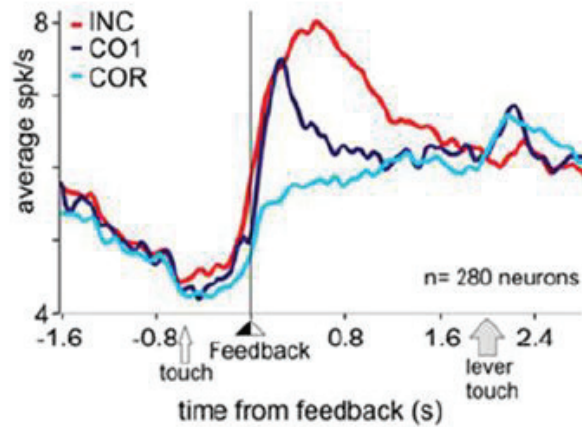


Fig. 2.4. Average MCC neuron activity as a function of time aligned to feedback. Red = incorrect answer during the search process, Blue = First correct answer, determines the end of the search, Light Blue = trials where the correct answer is repeated. The exploratory process trials, which involve finding the correct answer to the problem and therefore represent a state of uncertainty, show heightened MCC neuron activity when compared with the exploitation process, where the previously chosen positive results are repeated (Quilodran et al., 2008b).

2.3. MCC - LPFC Interactions

The MCC has been shown to process information that are relevant to regulate the flexibility or persistence of behavior, for instance information that indicate the need change behavior based on an objective (e.g. drop in recent gains). As described in the previous section, the MCC activity reacts to error and reward events that determine the change or maintenance of behavior. In addition, during the decision-making processes, it would be involved in the decision to explore alternative options, determining the degree of updating internal cognitive models that contribute to execute the current task (Kolling et al., 2016). However, an efficient and complete adaptive behavioral process requires more functions than those proposed here, and the MCC is strongly interconnected with the LPFC (Pandya et al., 1981) to which other complementary functions are attributed.

One of the first studies to report modulation of the LPFC by reward was Gemba et al (1997), demonstrating a modulation of the amplitude of potentials prior to movement. Subsequent studies showed that the LPFC modulates its activation according to previous results, especially in tasks in which performance in the current trial depends on the results of previous trials (Barraclough et al 2004). Recordings during the PST protocol have shown that spatial selectivity of LPFC single unit activity is regulated by the uncertainty of the response or outcome (Procyk & Goldman-Rakic, 2006) and a decrease in its general activity in the repetition periods of the test, a period associated with less engagement of cognitive control (Khamassi et al. 2014).

Studies based on brain imaging in humans have reported a functional coactivation of MCC and LPFC during the execution of cognitive tests (Locke & Braver, 2008; Hyafil et al. 2009; Duncan, 2013). The activity of these two regions correlated with uncertainty, as reported by Fleck et al (2006), where states of high uncertainty presented a greater response. Additionally these authors highlighted that only the MCC revealed a correlation of activation with reaction times, suggesting that this region performs a performance rating based on which the LPFC will react.

MCC - LPFC interactions have been given an important role to the process of monitoring and evaluating relevant behavioral feedback to trigger or engage specific adaptive strategies, including exploratory choices (Cavanagh and Frank, 2014; Khamassi et al., 2015; Kolling et al., 2018). Shenhav et al (2013) proposed a model in which the MCC integrates the information from the environment, processing it to calculate the need (value) for control that must be exercised at the level of the LPFC.

The work of Kolling & O'Reilly (2018) suggested that the neural dynamics in the MCC-LPFC interaction during decision making, which generate cognitive state changes allowing selection of the appropriate behavior, depend on the context. They underlined the importance and the influence of temporality, which defines when to act, and in combination to the evolving decision variables (e.g. reward rate minus cost rate), determines the behavioral changes.

Despite the theories and evidence presented by different studies, the specificity of how information is integrated within and between the prefrontal regions during decision-making still represents a pending challenge.

2.4. MCC and LFPC contribution to the decision to check

To study neuron dynamics and determine the mechanisms that contribute toward deciding to check in MCC and LFPC, Stoll et al. (2016) designed an experimental protocol to conduct a study in monkeys. The aim was to evaluate behavioral adaptability and the process of learning through a task that offers freedom in developing a personal strategy to decide to check.

The task design is based on a dual task principle (Fig. 2.5). At the start of each trial, the monkeys can choose the triangle stimulus to "Work" and perform a visual categorization task, or can choose the disk stimulus to "Check" and see whether a reward bonus is available, and if it is, then how far away they are from it. If they choose to work on the main task, they are shown a cue stimulus (a slanted bar to the right- or left-hand side with several possible angles, each representing one of the available difficulty levels). After a waiting period, they must respond by categorizing the direction of the cue by choosing a target to the right- or left-hand side (this Right versus Left decision is called a *Cued decision*). If the answer is correct, a small reward would be given. By contrast, choosing the disk stimulus provides information on how soon an additional reward would be offered, by way of a visual indicator, which gradually fills up as the test progresses. This additional bonus is awarded only if the monkey chooses to check when the gage is full. If the gage fills up, it remains full until the monkey checks the bonus option. Positive performance in the main task raises the indicator's level, thereby making the bonus closer to being delivered. In particular, the number of correct attempts required to obtain the bonus varies pseudo-randomly in successive blocks (after 14, 21, 28, or 36 attempts), and the indicator increases to 7 different levels. Therefore, one way of improving overall rewards is to perform well on the main task and also to check from time to time in order to gain information on bonus availability. Apart from the progress indicator that is shown at the

monkey's request, no explicit information is provided on the supposed need to check or assess.

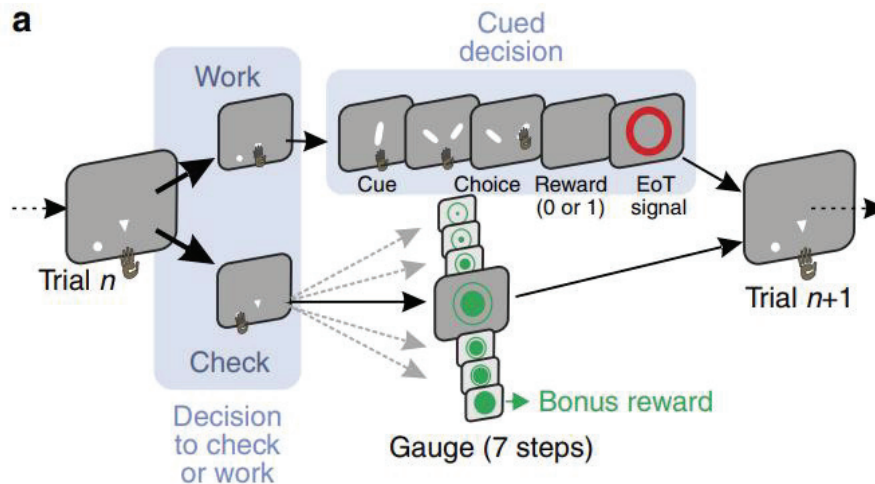


Fig 2.5. Experimental protocol. In each test, the monkeys can freely decide upon whether to work on a main task (where they are asked to perform a visual discrimination test that comprises categorizing a stimulus on the basis of the direction it inclines toward) or to check the status of the indicator that increases with the number of correct answers in the main task. The rate of increase is based on the total number of correct attempts required (four possible speeds). Deciding to check leads to a stimulus indicating task progress (a green disk with a circle that grows on the basis of correct answers in the main task). An additional reward is obtained after checking as soon as the indicator is complete. The indicator is reset after the additional reward is delivered (Stoll, Fontanier, et al., 2016).

The study quantified the differences between the two areas (MCC and LPFC) at the level of neuronal populations in Check/Work decisions and Decisions in the main task (Right/Left) using linear decoding (Fig. 2.6). The results of monkey recordings, as the monkeys went through their paces in this experimental protocol, through linear decoding latency, reveal that MCC leads LPFC in processing feedback and when deciding between checking and working. This relationship is inverted when deciding upon the direction of

the main test stimulus. Thus, we can predict that both areas exchange roles, depending on the situation or context.

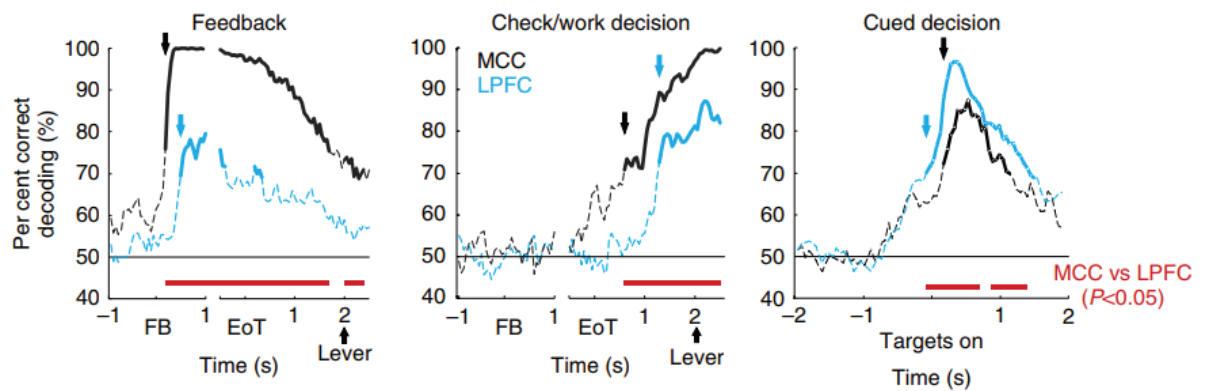


Fig. 2.6. Linear decoding for feedback processing, Check/Work decision and categorizing decisions in the visual discrimination test. The arrows indicate the first significant decoding for each area (color). The red line parallel to the graph's time axis indicates significant differences ($p < 0.05$). It indicates a double dissociation between MCC (black), which contributes earlier and more reliably in feedback processing and before the Check/Work decision, and LPFC, which codifies earlier and more reliably at the time of the main task's decision (Stoll, Fontanier, et al., 2016).

2.5. Oscillations and frequency evocations regulated by executive functions

Another relevant neurophysiological marker is oscillatory activity, which is described as a reflection of the basic communication mechanisms between distant brain regions (Buzsáki & Draguhn, 2004). The medial-frontal regions, including the anterior cingulate, indicate large theta oscillations (4 Hz–8 Hz) that, during cognitive tasks, are connected to regulating task requirements such as working memory, attention, and choosing an action (M. X. Cohen et al., 2007a; Tsujimoto et al., 2006; Wang et al., 2005). Theta-band components evoked by some stimuli have also been recorded within experimental protocols. Studies

have described increased power in this band after making mistakes when compared with the power in this band after providing a correct answer (De Pascalis et al., 2012; Marco-Pallares et al., 2008b). It could also regulate the reward probability, such that the lower the reward probability the greater the theta component's power (M. X. Cohen et al., 2007a). Other studies also showed changes in this low-frequency activity in response to positive feedback (Doñamayor et al., 2011b; HajiHosseini et al., 2012b).

With regard to communication between brain areas and transmitting information, an in-phase coupling between theta and gamma has been found (>30 Hz), in which low-frequency components regulate the transmission of high-frequency components in task requirements (Voytek et al., 2015). This event has also been associated with the need to maintain working memory (Roux & Uhlhaas, 2014).

In addition, beta-band components (20 Hz–30 Hz) with the same frontal–medial origin have been reported in response to positive feedback (Billeke et al., 2015; M. X. Cohen et al., 2007a; Doñamayor et al., 2011b; HajiHosseini et al., 2012b; Marco-Pallares et al., 2008b). In particular, Cunillera et al. (2012) used a modified version of the *Wisconsin Card Sorting Task* that includes the exploration and operation phases. They reported an increase in beta activity only for the first correct feedback in a series, without the subsequent repetition of the option. This discrimination effect with the information contained in the feedback, not only with its value, is seen in the FRN component (Quilodran et al., 2008b; Sallet et al., 2013a). Meanwhile, other studies have reported beta activity in response to negative feedback (Cohen et al., 2009; van de Vijver et al., 2011). A recent study reports the presence of beta components in response to both positive and negative feedback but regulated on the basis of the difficulty of the task performed. In low-difficulty tasks, an increase in the beta band's power was associated with errors or negative feedback. In contrast, high-difficulty tasks (error rate >30%) saw an increase in the beta band's power in response to positive feedback when compared with that in response to negative feedback (Billeke et al., 2020).

Studies have identified synchronization in the frequency range of the beta band in the prefrontal cortex in both roles: changing and choosing a strategy (Buschman et al., 2012) and maintaining cognitive control over time (Bastin et al., 2014; Stoll, Wilson, et al., 2016b). It was recently proposed that beta and gamma activities could be better understood

under burst activity mechanisms rather than oscillatory activity sustained for long periods (van Ede et al., 2018).

As for the FRN and beta components, the relationships with positive and negative feedback based on dopamine modulation remain unclear. Because of the nature of the firing of dopaminergic units, where there is an inhibition of these neurons for negative errors in the prediction error and an activation for positive ones (Schultz, 2007), it was suggested that the effect of positive prediction errors is stronger in FRN than the effect of negative prediction errors is (Clay B. Holroyd et al., 2008). However, the activity recorded in MCC has repeatedly shown that the neuronal populations that contribute to processing negative and positive results are separated (Kennerley et al., 2009a; Matsumoto, Matsumoto, Abe, et al., 2007; Quilodran et al., 2008b).

2.6. Parkinson's disease and its variations in neurophysiological markers

The global population's increasing average age is inherently linked to increased neurodegenerative diseases. These diseases involve a series of physical, emotional, and cognitive correlations, not always studied in all dimensions. With regard to Parkinson's disease (PD), motor variables have been studied more than cognitive and emotional ones. Therefore, the efforts to understand the disease and treat it have particularly shown results in the motor aspects. This means that the presence, detection, and treatment of cognitive symptoms in PD has not been considered until very recently. It is now one of the current challenges of the scientific community.

PD is a degenerative condition secondary to decreased dopamine in the basal ganglia (Dauer & Przedborski, 2003; Rodriguez-Oroz et al., 2009a). PD affects approximately 1% of the population over 60 years old (de Rijk et al., 2000). The WHO estimates that by 2025, 3/4 of the 1.2 billion people over the age of 60 will reside in developing countries. Therefore, neurodegenerative diseases in adults and older adults are a public health

problem, which must be managed with appropriate policies by the health authorities in our country.

PD has traditionally been considered a motor disorder. The main symptoms are tremors while at rest, bradykinesia (slowness in starting, performing, or completing voluntary movement), rigidity, and progressive postural challenges (Hoehn & Yahr, 1967b). It is now recognized that patients with PD also present cognitive dysfunctions, even in the initial stages of the disease (Koerts et al., 2009; Leverenz et al., 2009; Muslimovic et al., 2005b). Cognitive impairment is primarily concentrated among executive functions (Leh et al., 2010; Monchi et al., 2007).

The clinical implications of this disease can be seen at the motor, cognitive, and emotional level. However, the paradigm that must be addressed regarding this disease concerns its onset as well as the progression of symptoms. Currently, clinical diagnosis requires the presence of at least two major motor symptoms from the classic triad: i) tremors at rest; ii) rigidity; and iii) bradykinesia (Hughes, Daniel, et al., 1992; Nutt & Wooten, 2005; Olanow & Obeso, 2012b). However, clinical pathology studies from the United Kingdom Parkinson's Disease Society Brain Bank (UKPD) indicate that the clinical diagnosis can be made with greater precision when those suffering from Parkinson's have an asymmetry of motor deficits and a good response to levodopa, in addition to resting tremors (Hughes, Ben-Shlomo, et al., 1992).

One of the non-motor symptoms that affect between 1.7% and 7% of PD patients who are treated with dopamine agonists is pathological gambling (Weintraub et al., 2015), which is already commonly considered a side effect of treatment (Voon et al., 2011). However, important aspects that affect patients' quality of life, such as hypersexuality, compulsive shopping, and compulsive eating, are also reported. As they are non-motor symptoms, they can occur prior to the pathological diagnosis.

There is extensive evidence of electrophysiological markers linked to cognitive control to different degrees that reportedly decrease in PD patients when compared with the control population (Seer et al., 2016). However, we will continue to focus on possibilities that reflect the performance of executive functions and adaptive behavior.

Studies that analyze ERP in the Go/No-Go task reported a trend toward reduced P3a potential in studies (Christian Beste et al., 2009; Osawa et al., 2005) that analyzed PD

patients taking medication, but the study carried out in the OFF state did not report significant differences (Christian Beste et al., 2010). However, reasonable integration of these data between studies is difficult because of the heterogeneous study designs and ERP measures. Despite this, the results are not very conclusive because of the heterogeneous measurement methods (Seer et al., 2016).

The variations presented in N2 potential are even less conclusive and require further study. Until now, the evidence has suggested that they could be related to early stages of PD. A study among carriers of the Parkin or PINK1 mutation, who are considered asymptomatic PD patients in the preclinical stage, detected reduced N2 potential (Verleger et al., 2010). The same effect is presented in new patients who have been recently diagnosed and do not have established treatment (Willemsen et al., 2011).

Experimental protocols that evoke the ERN potential provide more substantial evidence for reduced executive functions in PD. Considered together, the data reviewed from ERN studies indicate that both insufficient and excessive levels of dopamine impair performance monitoring in PD (Seer et al., 2016). On the left-hand side of Figure 8, the results of the average FCz electrode signal (front–central) in the flanker paradigm for the correct and incorrect response conditions (dotted and solid lines, respectively) for novo PD patients and their control group (red and green) appear. They show decreased signal ranges in response to an error in novo PD patients when compared with those seen in the control group. These results are consistent with those of other studies (C. Beste et al., 2009; Falkenstein, Hielscher, et al., 2001b; Rustamov et al., 2014). In contrast, two studies report no change in the range of ERN among PD patients.

The study by Martinez-Horta et al. (Martínez-Horta et al., 2014) that compares ERP in response to positive and negative feedback between apathetic and non-apatetic PD patients reports a significant reduction in FRN among patients with high levels of apathy. Brown et al. (2020) compared PD patients in the ON and OFF state of medication with a control group (see Figure 8, right). The results reflect reduced RewP between PD patients (in both states) when compared with its levels in the control group. There was no significant difference between the ON/OFF states among the patients.

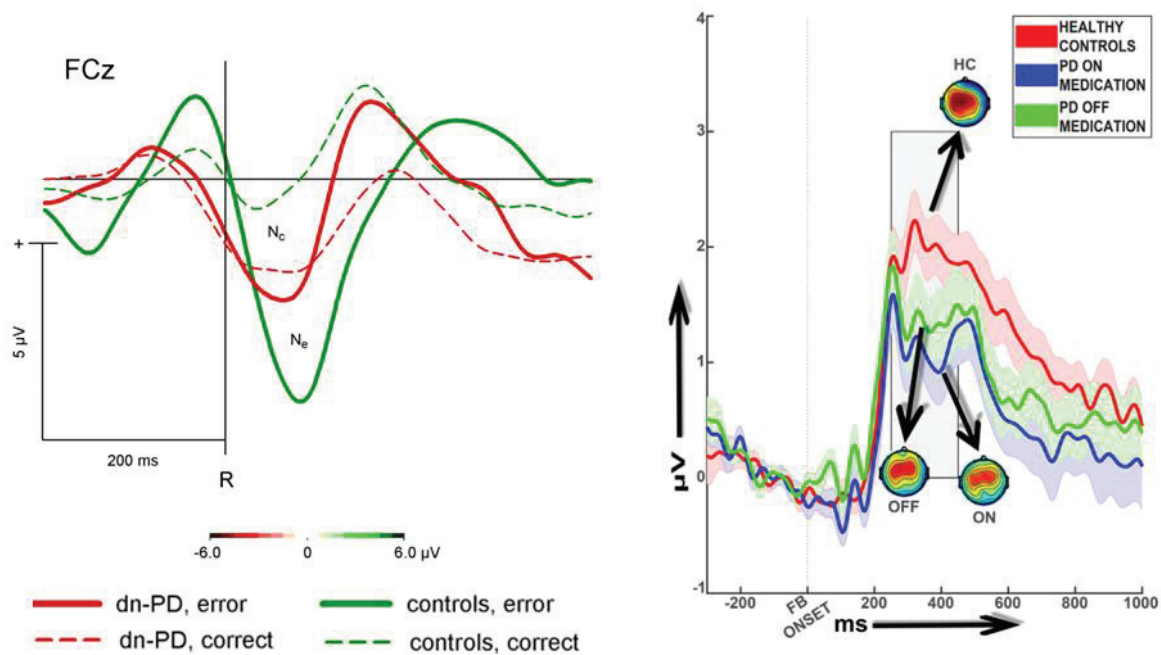


Fig. 8. Variation of potentials related to executive functions in Parkinson's disease. (Left) ERN of patients recently diagnosed with PD: control signals (green) and PD patients (red) are shown centered at the time of response, distinguishing between correct (dotted line) and incorrect (solid line) responses. The left-hand side panel demonstrates that patients with early PD show decreased ERN potential and a loss in the difference between possibilities generated by correct and incorrect responses (image modified from (Willemsen et al., 2009a)). (Right) ERP focused on the appearance of feedback: for the healthy control group (red), the PD patients under medication (blue) group, and the group without the effect of medication (green). It shows a decrease in PD patients when compared with its levels in the healthy control group and the group with no effect on medication status (Brown et al., 2020a).

If frontal–medial theta activity is established as a mechanism of cognitive control (Cavanagh & Frank, 2014) and a reflection of dopaminergic activity, a decrease in this activity among PD patients as well as in the evoked potentials is expected. Studies report this decrease in theta activity before tests that present a change (Cavanagh et al., 2017; Chen et al., 2016; J. Kim et al., 2017) and in cognitive control tests in response to conflict (Singh et al., 2018a). A different effect is reported in a study comparing PD Gamblers, PD Non-Gamblers, and a control group, where frontal theta activity is increased in PD Gambler patients in comparison with the activity levels in the other two groups (Balconi et

al., 2018). Pathological gambling is one more reflection of the fact that the information process in response to an action or feedback is altered. Patients are unable to stop when playing at a casino despite losing, even leading to economic debt, which reflects the loss of reaction and rethinking behavioral strategies.

Theta activity also reportedly specifically affects apathetic PD patients when compared with non-apathetic ones. There is a significant decrease in the theta and alpha bands (Zhu et al., 2019), which aligns with the decrease in ERP reported by Martinez-Horta et al. (2014)

Through a monkey model of PD, changes in frontal beta power have been reported, reflecting reduced commitment when completing a trial-and-error resolution test and the PST—behavior that is induced by a progressive lesion of the dopaminergic system (C. R. E. Wilson et al., 2016). In the literature, more evidence is reported of beta activity connected to the regulation of movement. Certain studies link this activity to maintaining the status quo for new movements, detecting increased beta activity after the execution of a response (Benis et al., 2014; Little & Brown, 2014), presuming the possibility of reflecting a rapid brake signal, and inhibiting an inappropriate motor response (Frank et al., 2007; Swann et al., 2011). This increase has also been found in reinforcement learning tests after response (Schroll et al., 2018a). Excessive beta activity could explain the signs of bradykinesia in Parkinson's patients (Little & Brown, 2014).

The first part of my project seeks to evaluate PD patients in the OFF state (without the effect of drugs) in the early and middle stages of the disease, using EEG recordings while performing the PST protocol and contrasting their performance with that of a control group. The characteristics of this protocol allow the exchange of states between exploration and exploitation to be studied in addition to the response in the frontal–central electrodes because of different feedback to adapt behavior, indirectly evaluating the role of dopamine in these processes.

2.7. Obsessive Compulsive Disorder and variations in neurophysiological markers

Obsessive compulsive disorder (OCD) is characterized by persistent, intrusive, and distressing obsessions or compulsions. It is associated with marked changes in quality of life because of its dysfunctionality (American Psychiatric Association, 2013). It was initially categorized as a disorder of uncertainty (Reed, 1977) because of the high levels of indecision characterizing those who suffer from it, along with impaired efficiency in decision-making, which includes insignificant decisions (Tolin et al., 2003). The key characteristics of OCD are this indecision, an intolerance to uncertainty (Holaway et al., 2006; Sarawgi et al., 2013), and a more cautious decision-making style (Volans, 1976).

The Tower of Hanoi, which is a neuropsychological test sensitive to the frontal–striatal circuit’s functioning and damage to the basal ganglia, has shown changes in OCD (Cavedini et al., 2001; Mataix-Cols et al., 1999). Meanwhile, the Object Alternation Test could reflect a defect in OFC (Cavedini et al., 1998; Gross-Isseroff et al., 1996). Clinical observations of OCD patients describe pathological behaviors related to the non-adaptive perception of rewards, where repeatedly and systematically performing an activity does not stop despite having achieved the objective, for example compulsive handwashing, without being able to perceive that the signal for this need is no longer present (Phillips et al., 2000). In the absence of adaptive behavior, which produces the continuous repetition of an action, a relationship that seeks an immediate reward is established, alleviating anxiety from the compulsion at the cost of a future penalty—diminished quality of life (Cavedini et al., 2006).

The studies regarding decision-making of patients with OCD are not conclusive. Some studies using the Iowa Gambling Task (IGT) have reported a reduction in the score obtained in this test (Cavedini et al., 2010, 2012; Kashyap et al., 2013), while others report poor performance only among patient subgroups (Lawrence et al., 2006; Nielen et al., 2002). Meanwhile, some studies indicate a dissociative nature, showing deficits in making unclear decisions but not risky ones (Kim et al., 2015).

The indecision and excessive caution that characterize OCD patients can trigger a greater need to collect information and therefore increase the frequency of checking (Hauser et al., 2017; Voon et al., 2017) although this has not been confirmed in all studies

(Grassi et al., n.d.; Jacobsen et al., 2012). Excessive caution in decision-making can provide better performance in tasks where a longer time to obtain a response has a low cost (Hauser et al., 2017).

Patients with OCD have been shown to show a hyper-reactive learning and monitoring system (Ullsperger et al., 2014), leading to higher error-related brain potentials (ERN) (Cavanagh et al., 2010; Endrass & Ullsperger, 2014; Xiao et al., 2011). This finding is supported by fMRI evidence, revealing hyper-responsiveness from the ACC in such patients (Fitzgerald et al., 2005; Hauser et al., 2017; Maltby et al., 2005). It is not only the ERPs that are altered in OCD patients; Bastin et al. (2014) showed changes in oscillatory patterns in the delta–alpha frequency range (1 Hz to 12 Hz) in the sub-thalamic nucleus, using Local Field Potential (LFP) recordings, that could reflect compensatory strategies to maintain stable motor, cognitive, and emotional functions. These are recorded as abnormally high, particularly in the left hemisphere in cases of acute OCD.

Despite the worldwide prevalence of OCD at 2% to 3%, its neurobiological origin is still unclear, demonstrated in experimental studies suggesting that it could reside in the uncontrolled activation of frontal–striatal circuits. Understanding the mechanisms that prompt checking and searching for additional information becomes relevant in order to understand this pathology that affects the quality of life of many people. The second part of my project arises in this context, which uses the experimental protocol designed by Stoll et al. (2016) and adapts it to humans and a control population. This protocol offers the freedom to decide when to complete the check, enabling analysis of the strategy that subjects develop, and to use electroencephalography to study neurophysiological events that arise, focusing on communication between the medial and LPFC.

3. Practical Aspects in Biomarker Study Methods

To study electrophysiological biomarkers, particularly using the EEG technique, it is necessary to use processing techniques that improve the signal/noise ratio of our data. In this process, poor choices can lead to distortions in the time or extent of the study signals, which will be reflected in poor interpretation of the results.

There are different preprocessing guidelines that aim to establish a common standard for EEG studies (Bigdely-Shamlo et al., 2015; Debnath et al., 2020; Gabard-Durnam et al., 2018; Mognon et al., 2011; Nolan et al., 2010). Each version adapts the processes to its experimental protocol and the study subjects, but they preserve the following main stages:

- Filtering
- Baseline removal
- Artifact removal (such as EOG and EMG)
- High noise channel rejection and interpolation

In this section, I comment on some practical aspects that impact the signal, focusing on studying ERPs and oscillations on the basis of the use of the Matlab analysis platform and the FieldTrip Toolbox (Oostenveld et al., 2011a).

3.1. Filtering effects on the signal

The filtering stage is one of the most common. It is also one of the most essential processes in neuroscience as a poor choice in filtering can generate reduced and temporary shifts of events.

In general, filters can be classified as responding to a finite impulse response (FIR) or infinite impulse response (IIR). FIR filters are more stable and cause fewer nonlinear distortions at this stage, but their computational costs are higher (M. Cohen, 2014; Handy, 2005). The default selection in FieldTrip is a Butterworth IIR filter, which has a minimum cutoff frequency of 1 Hz because the filter is unstable under this value.

The minimum cutoff frequency value can have a significant impact, depending on the type of signal and the type of analysis to be conducted, particularly when applying the high-pass filter used to eliminate the drift of the nonstationary signal through the recording. Some authors suggest that the cutoff frequency value of the high-pass filters should be as low as possible or the range of the ERPs may be altered (Acunzo et al., 2012; Kappenman & Luck, 2010; Maess et al., 2016; Tanner et al., 2015). Kappenman (2010) analyzed the effect of the cutoff frequency of the high-pass filter at controlled temperature, quality, and humidity in high-impedance records, demonstrating a progressive reduction of possibilities on the basis of the increased cutoff frequency (Fig. 3.1.C). In contrast, other authors report that high-pass filters with a cutoff frequency lower than 1 Hz are detrimental to analysis based on ICA because low frequencies distort their results (Bigdely-Shamlo et al., 2015; Gabard-Durnam et al., 2018).

To determine the cutoff frequency to be used, it is advisable to know the characteristics of the signal to be analyzed, especially in reference to the signal-to-noise ratio measurement. We evaluated the effect on the average ERP among 502 trials recorded during the PST test, with unit AgCl electrodes. This facilitates obtaining low amplitudes because the electrode area can be cleaned with greater precision than by using the acquisition helmet for the purpose. No effect was observed on the range of possibilities based on the cutoff frequency of the FIR filter (FIRws) used (Fig. 3.1.A). A lower cutoff frequency in the FIRws filter is characterized by a higher order in the filter (Fig. 3.1.D). This, in turn, leads to higher computational requirements, which can be seen in the processing time it takes to execute the tasks (Fig. 3.1.B). If the processing time is important and the quality of the recordings allows for it, using a Butterworth filter can reduce processing time by 16.6% by selecting a cutoff frequency of 1 Hz. The calculation is made on an HP Z800 machine with a dual Intel Xeon 2.66 GHz processor, 24 Gb RAM with 24-channel data, 256 Hz sampling frequency, and trials in a 3-second window.

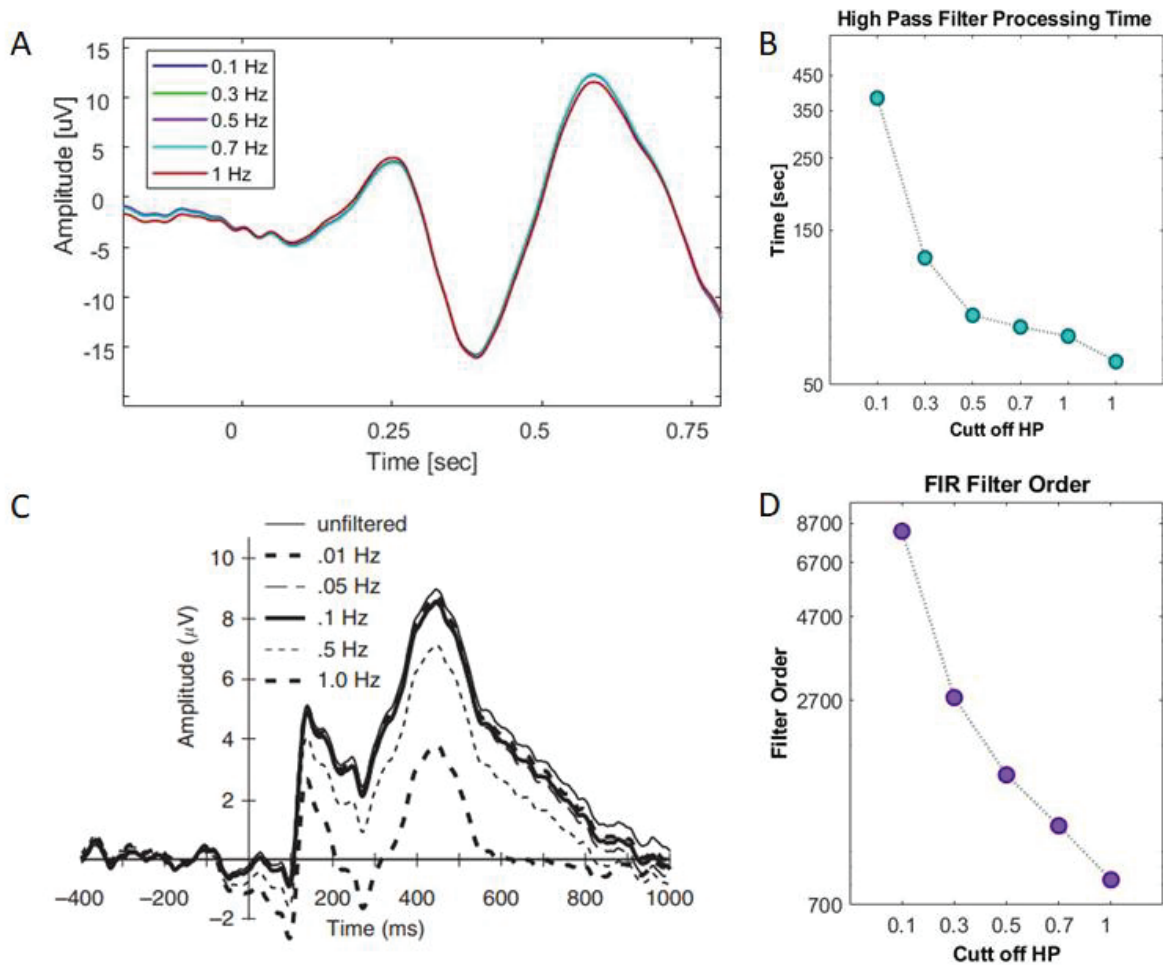


Fig. 3.1. High-pass filter effects. (A) Average ERP of 502 trials sampled at 256 Hz and focused on the appearance of the frontal electrode feedback, using windowed FIR filters, low passes with a cutoff frequency of 30 Hz, and high passes at different cutoff frequencies. (B) Processing times and (D) order of the windowed FIR high-pass filter of the FieldTrip `ft_preprocessing` function, with a variant in the cutoff frequency of the high-pass filter on an HP Z800 computer with dual Intel Xeon 2.66 GHz processor and 24 Gb RAM. (C) Average ERP as a function of the cutoff of the high-pass filter in the parietal electrode under high-impedance conditions (Kappenman & Luck, 2010).

To avoid distortions in the short-term, it is important to use one-pass zero-phase filters, which momentarily add zeros to avoid displacement when applying the filter or when applying it twice to cancel the displacement when applying it in the opposite direction a second time. By default, the function `ft_preprocessing` uses double application with

opposite directions for the filter, except with the FIRws filter where application of the zero-phase option is set by default.

3.2. Wavelet versus Hilbert Transform

To study both the frequency components of the ERP as well as oscillations, and even the analysis of phase coherence, the Wavelet or Hilbert transform is commonly used. Le Van Quyen (2001) shows that both transforms present similar results in neuronal synchrony analysis. However, to understand their practical differences, a performance test was completed against a simulated signal comprising 3 oscillations at 4 Hz, 10 Hz, and 30 Hz in different time frames with a sampling frequency of 1,024 Hz (Fig. 3.2.A).

Obtaining the time–frequency decomposition of the signal (Fig. 3.2.B) depends on a certain parameter w , which expresses the relationship between time and frequency. A low value, for example, $w = 3$ (Fig. 9.B, left) provides temporal precision over the frequency, and the parabolic effect of the low frequencies is lesser. In contrast, a parameter $w = 12$ (Fig. 9.B, right) determines the power of the frequencies better. The effect stands out in the high frequency, showing a better-defined appearance, but the parabolic effect cancels many values in the low-frequency scale. This can be solved by selecting an extended analysis window such as -3 to 3 seconds instead of -1 to 2 seconds focused on the appearance of feedback. Another complementary method involves adding frequencies to the analyzed vector (cfg.foi). Instead of choosing 50 frequency values between 3 Hz and 50 Hz, select 100 values. This increases the amount of data processed, and with it increases the time for future processing and required storage. A recommended w value to balance time and frequency band resolution is 6 or 7 (Lachaux et al., 1999) (Fig. 3.2.B, center).

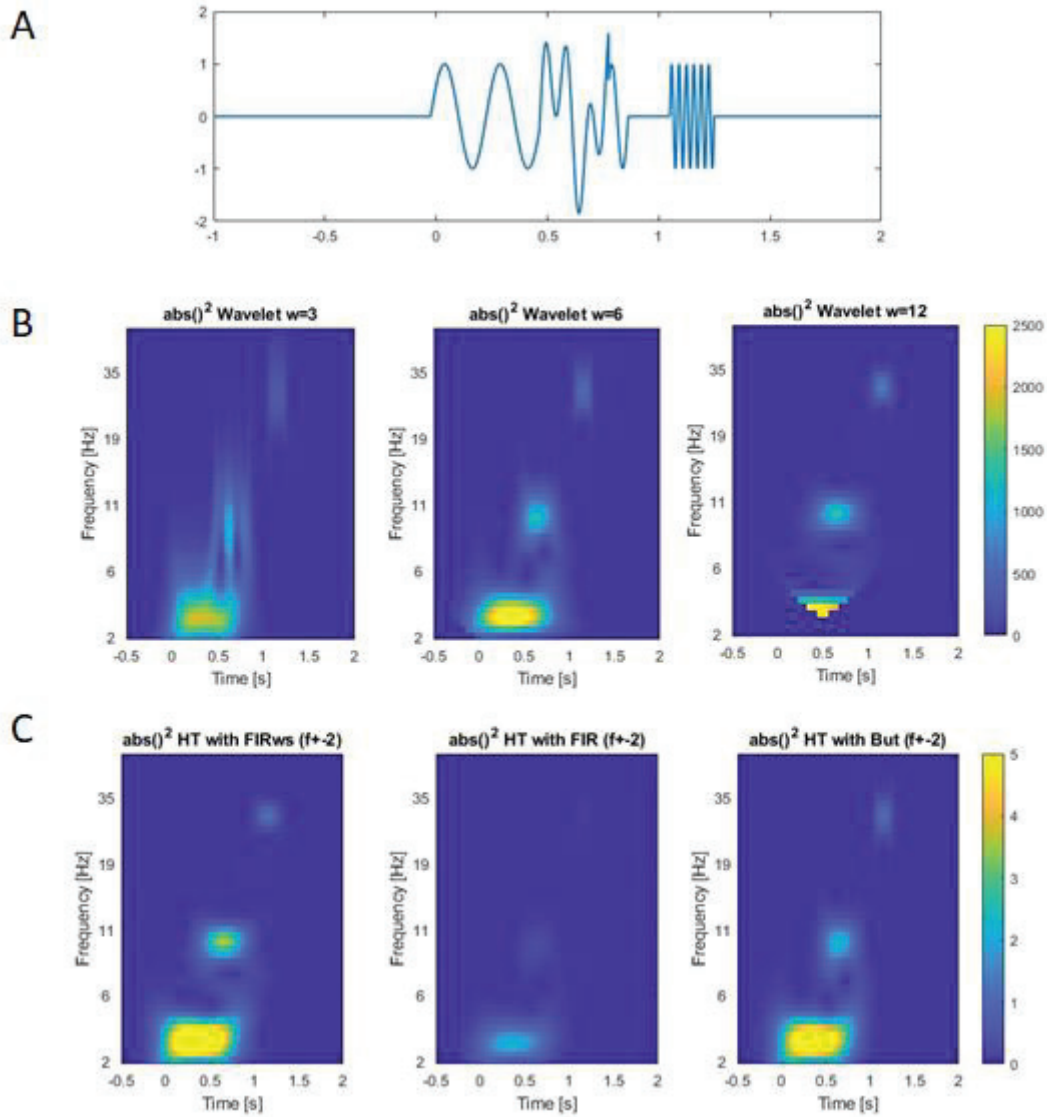


Fig. 3.2. Simulation to evaluate the performance of the Hilbert and Wavelet transform. (A) 3-second simulated signal at 1,024 Hz sample rate with components: 4 Hz between 0 and 0.8 sec., 10 Hz between 0.5 to 0.9 sec., and 30 Hz between 1 and 1.2 sec. (B) Applying the wavelet transform to different wave widths in number of cycles (w). Choosing a small value aids in temporal resolution, thereby sacrificing resolution in frequency, whereas a higher w value reverses this effect and increases the parabolic value in low frequencies. (C) Application of the Hilbert transform using different filters with cutoff frequency $f \pm 2$ Hz.

To obtain the frequency decomposition using the Hilbert transform, a filter that performs the selection of the band being analyzed must be used. Thus, using the same $f \pm 2$ Hz band selection, the FIRws (Fig. 3.2.C, left), FIR (Fig. 3.2.C, center) and Butterworth (Fig. 3.2.C, right) filters are assessed. The difference between the two FIR filters is the complementary use of a windowed filter (Hamming by default) that reduces dispersion at the edges of the FIR filter by itself. If the FIRws filter is purchased with the Butterworth filter, greater definition can be seen in the temporal and frequency periods of the events. The simulation reflects results obtained by Cohen (2014), who indicates that in decompositions for time–frequency, the FIR filters are preferable to IIR ones.

The choice of parameters at each stage of the study's signal preprocessing can create variation that leads to erroneous conclusions. Knowing the acquisition and analysis protocols is essential to interpreting our results correctly and thereby allowing us to achieve this project's objective. Specifically the project is the study of neurophysiological markers originating in the prefrontal cortex that reflect adaptive functions in humans, particularly changes between exploration and exploitation, and information search in decisions to check.

4. Experimental studies

Goal-directed behavior involves a constant interplay between searching for information or strategies that open the paths leading to goals, i.e. exploration, and the use of this information to repeat successful behaviors, i.e. exploitation. To regulate the balance between the two, brains have evolved a monitoring system that monitor and evaluates information received from interactions with the environment, and detects changes allowing rapid corrections depending on the objective. This monitoring system is not limited to processing information it receives from action-outcome interactions, it apparently also contributes to initiate information seeking. Information seeking contributes to goal-directed behavior by permitting the verification of progress towards goals, the reduction of uncertainty, and the reduction of the likelihood of future errors. It thus helps improving performance. However, the nature of the performance monitoring mechanism is not fully understood and its relationships with exploratory or verification behavior remains to be explored. In addition, the neural correlates of those two components could serve as markers of certain pathological conditions affecting performance monitoring functions.

In this section I will present the EEG experiments and analyses carried out during my thesis work, to evaluate this monitoring and control system that allows adaptive behavior in humans, from two perspectives:

Experiment 1: Feedback-related potentials and oscillations during trial and error learning in Parkinson's disease patients.

A study of neurophysiological responses to feedback during exploration and exploitation in Parkinson's disease. The feedback-related negativity (FRN) is an event-related potential, classically associated to the mid-cingulate cortex, and corresponding to a phasic response to negative or positive performance feedback. Recently, theta activity at the time of feedback has also been associated to processes similar to the FRN and beta activity to response to positive feedback. These markers seem to have a relationship with learning and the dopamine system. In this first part of my project I analyzed the FRN and EEG oscillations elicited by positive or negative feedback in a trial-and-error problem solving task assessing exploratory behavior and exploitation in control subjects and in patients with Parkinson's disease.

Experiment 2: Human frontal neural dynamics reveal strategies for performance monitoring and decisions to check.

A study of neural dynamics in human EEG related to the regulation and motivation of decisions to check. Information seeking is one major behavioral activity in humans. For instance, verification or checking is common to many adaptive activities, serving to potentially increase the efficiency of decisions and to reduce uncertainty about outcomes. The neurobiological bases of decisions to check rely in part on the frontal cortex which might have a role in controlling and regulating the impulse to check. The second part of my project addressed the question of the neural bases of decisions to check for information, and in particular the dynamics in frontal brain regions that contribute to these decisions. We performed EEG recordings in young and healthy human subjects in an experimental task that challenged the checking process using positive and negative reinforcements. We seek to explore the course and relationships between markers of outcome monitoring and those related to decisions to check.

4.1. Feedback-related potentials and oscillations during trial and error learning in Parkinson's disease

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ABSTRACT

Electrophysiological markers of performance monitoring are thought to reflect functioning of dedicated neural networks and neuromodulatory systems. Whether and how these markers are altered in neurological diseases and whether they can reflect particular cognitive deficits remains to be confirmed. Here we first tested whether the frontal medial feedback-related potential, evoked during a trial and error learning task, is changed in early Parkinson's disease patients compared to control subjects. The potential was not changed in amplitude and discriminated negative and positive feedback as in controls. Feedback-related markers in Parkinson's patients also appeared in time-frequency analyses, unaltered in theta (3-7 Hz) band but reduced in beta (20-30 Hz) oscillations for positive feedback. Beta oscillations power appeared to be dramatically globally reduced during the task. Overall, our results show that Beta oscillation markers of performance monitoring captured by EEG are selectively altered in Parkinson's disease patients, and that they are accompanied by changes in task-related oscillatory dynamics.

SIGNIFICANCE STATEMENT

Frontal neural activity evoked by outcomes reveal the functioning of neural systems devoted to flexible behaviours. Modulations of such activity in Parkinson's disease (PD) patients could reflect specific alterations of neural systems and cognitive processing. The goal is to evaluate whether such activity can serve as markers of the disease. Here, using EEG and a trial and error learning protocol, we show that mid-frontal midline performance feedback-related potentials for different types of feedback were similar in controls and early diagnosed PD patients. However, task-related oscillations revealed alterations in the beta range accompanied by more global beta activity alteration in PD compared to controls subjects. This study provides data relevant to the search for non-motor biomarkers in early stages of PD.

INTRODUCTION

Besides the cardinal clinical features of Parkinson's disease (PD), including dysfunctions of the somatomotor system, non-motor symptoms develop in the early stages of PD and might often precede motor disabilities (Del Tredici & Braak, 2012; Rodriguez-Oroz et al., 2009b; Simuni & Sethi, 2008). These symptoms encompass impairments of executive functions, and neuropsychiatric (e.g. apathy, depression) or sleep disorders. Executive impairments, are important predictors of quality of life (Schrag et al., 2000), and are present in a large proportion of patients with PD (20-40%) at initial diagnosis although they are often overshadowed by motor symptoms (Foltynie et al., 2004; Muslimovic et al., 2005a). Disabilities for planning and adapting behavior, or evaluating outcomes of actions are some of cognitive dysfunctions observed in PD (Cools et al., 2001; Dirnberger et al., 2005; Owen et al., 1992). Identification of markers of Parkinson's disease would be beneficial for early detection and early therapeutic interventions, and their potential relationships to behavioral or cognitive alteration would help understand the evolution of the disease.

Two well studied markers of performance monitoring are the error-related negativity (ERN), an event-related potential evoked at the execution of incorrect responses in

reaction time tasks, and the feedback-related negativity (FRN) observed after the presentation of a sensory feedback signaling performance (Sallet et al., 2013b; M. Ullsperger et al., 2014). One possible central source of the FRN is the midcingulate cortex (MCC), a cortical region receiving important mesocortical dopaminergic input and involved in feedback processing (Procyk et al., 2016; S. Williams, 1998). The Reinforcement Learning theory of the ERN causally links these markers to the dopaminergic system and the MCC (Clay B. Holroyd & Coles, 2002b). Recordings in monkeys MCC revealed that some aspects of feedback-related single unit activity are modulated in accordance with reinforcement-learning like rules, but others seem to relate more to feedback categorizations and the expression of switch-stay behavioral strategies (Matsumoto, Matsumoto, & Tanaka, 2007; Quilodran et al., 2008a). One assumption is that performance monitoring signals (FRN or ERN) correlate with the state of dopaminergic transmission (Jocham & Ullsperger, 2009). This has been tested pharmacologically in non-human primates for FRN (Vezoli & Procyk, 2009a; C. R. Wilson et al., 2016) and in humans (P J Zirnheld et al., 2004). In a progressive and pre-symptomatic monkey model of Parkinson's disease, the FRN was the most altered marker of the lesion, although this effect was found in the absence of behavioral deficit in a deterministic trial and error learning task (C. R. Wilson et al., 2016). Several EEG studies have demonstrated amplitude attenuation of the ERN in PD patients (Falkenstein, Hielscher, et al., 2001a; Ito & Kitagawa, 2006; Willemsen et al., 2009c) whereas other studies did not, depending on the tested group or medication status (Clay B Holroyd et al., 2002; Stemmer et al., 2007). Note importantly, that the FRN can be associated to both negative and positive feedback of performance (Sallet et al., 2013b). However, to our knowledge there are only rare studies investigating FRN modulations in PD patients. One recent study showed that a fronto-central positivity to positive Feedback was diminished in PD patients compared to controls in a probabilistic two alternative forced choice task (Brown et al., 2020b). The reward-related potential did not vary with ON-OFF status of medications, but was more reduced for early compared to later diagnosed patients. Finally, the FRN for negative outcomes (no reward) did not vary between subject groups.

Other relevant neurophysiological markers are oscillation power evoked or induced during tasks and that might reflect basic mechanisms of communication, processing, and

might contribute to plasticity (Buzsáki & Draguhn, 2004a). Theta and beta oscillations have been observed after negative and/or positive outcomes or feedback (M. X. Cohen et al., 2007b; De Pascalis et al., 2010a; Doñamayor et al., 2011a; HajiHosseini et al., 2012a; HajiHosseini & Holroyd, 2015; Marco-Pallares et al., 2008a; Marco-Pallarés et al., 2009; van de Vijver et al., 2011a). Investigations have shown important alteration of subcortical beta oscillations in PD patients in relation to sensorimotor events but also to reinforcements (Schroll et al., 2018b). In addition, alterations of oscillation power measured by EEG in PD patients have been observed at low frequency (delta and theta bands) during cognitive tasks and compared to age-matched healthy controls, suggesting that altered signal in those bands (especially on the frontal midline) might be used as a biomarker of dysfunction in Parkinson's disease (Schmiedt-Fehr et al., 2007; Singh et al., 2018b).

The relationships between FRN, outcome-related oscillations, positive and negative feedback processing and Parkinson's disease thus remain unclear. Because of the asymmetric nature of dopaminergic single unit firing for negative (inhibition) and positive (activation) prediction errors (Wolfram Schultz, 2007b), it was postulated that the effect of positive prediction errors is stronger on FRN than negative prediction errors (C B Holroyd et al., 2008). However, studies of single unit activity in MCC have repeatedly shown that single unit populations contributing to negative versus positive outcome processing are separated (Kennerley et al., 2009b; Matsumoto, Matsumoto, & Tanaka, 2007; Quilodran et al., 2008a). Alternatively, the FRN (and its variance explained by outcome value) is also conceived as a reward positivity acting on top of, and reducing, a generic negative deflection observed for other events including negative feedback (C B Holroyd et al., 2008; Proudfit, 2015). This alternative would indeed suggest two separate sources.

The alteration of these features in Parkinson's disease is poorly described. Here we used a behavioral protocol involving robust adaptive components (trial and error learning task) to test the potential modifications of FRN and oscillatory activity in the beta and theta bands by altered dopaminergic states in Parkinson's disease. We took advantage of some properties of the protocol (various forms of negative and positive feedback) to study the modulations of FRN and oscillations in Parkinson's disease patients compared to

control subjects, and to test whether the altered neural states in patients would differentially influence frontal responses to positive and negative feedback.

METHODOLOGY

Participants

Seventeen patients with idiopathic PD and fifteen age-matched healthy controls participated in the study. All participants gave signed informed consent according to the declaration of Helsinki after they were introduced to the purpose of the study and after the protocol was explained to them. The study was performed with the approval by the review boards and the School of Medicine's ethics committees.

The patients were recruited at the Department of Neurology and Parkinson's disease Health Center, and the diagnosis of PD was based on the clinical criteria of the United Kingdom Parkinson Disease Society Brain Bank (UPKD) (Daniel, 1993). The mean age of the patients was 64.9 +/- 7.1 years (+/- SD). Diagnosis of PD was made on average 4.9 years before EEG recordings. All patients were receiving L-dopa therapy and were selected for being at clinical stage 1-3 using Hoehn and Yahr classification (HYS) i.e. they were at the initial stages of the disease (Hoehn & Yahr, 1967a), mean 2.4 +/-0.6. Motor status and quality of life were determined by the motor subscale of the UPDRS (Fahn & Elthon, 1987; Goetz et al., 2008), with evaluation of 37.3+/-16.3, and PDQ-39 test (30+/- 17.6). During experimental sessions, all patients were in OFF medication (medication was stopped on the evening prior to the experiment; the experiment was performed in the morning; medication was re-initiated after the test). Each patient's medication was checked and doses of antiparkinsonian medication were converted to levodopa equivalent daily dose (LED) according to the algorithm used in Tomlinson and colleagues (Tomlinson et al., 2010).

None of the patients had dementia, history of cerebral infarction, pronounced tremor or presence of atherosclerosis. The mean age of control subjects was 65.9 +/- 6.6 years (+/- SD). None of the selected control subjects had any history of neurological or

psychiatric disorder (no history of dementia, no cognitive deficit tested ensuring ACE-R < 74/100, a BDI-II depression score < 18, and an apathy score (AS) < 14) and none of the subjects was taking drug affecting the central nervous system. All participants were right-handed. All subjects were assessed with a series of neuropsychological tests in a separate session before EEG recording to investigate participant's cognitive and emotional status. Cognitive functions were estimated using the revised version of the Addenbrooke's Cognitive Examination (ACE-R) (Larner & Mitchell, 2014), controls: 91.7 +/- 5.5 and PD patients: 86.55 +/- 6.6 (1-way ANOVA on Subject Group effect, $F(1,30)=6.68$, $p = 0.015$). Apathy and depression were evaluated using the Apathy scale (AS) (Starkstein et al., 1992), control: 4.2 +/- 2.9 and PD patients: 11.1 +/- 7.3 (1-way ANOVA, $F(1,30)=13.06$, $p = 0.001$), and the Beck Depression Inventory – Second Edition (BDI-II) (Beck et al., 1987), control: 10.5 +/- 6.1 and PD patients 13.8 +/- 9.1 (1-way ANOVA, $F(1,30)=1.46$, $p = 0.26$). The two groups of subjects thus differed in terms of apathy score, and cognitive and education level scores.

Behavioral protocol

To assess executive functions and markers of behavioral adaptation we used electroencephalography (EEG) while participants were performing a modified version of a trial and error task. Each subject was comfortably seated in an armchair at 100 cm in front of a 21-inch monitor screen, on which visual targets were presented using E-Prime 2.0 Professional Edition (Psychology Software Tools, Pittsburg, PA, USA).

During the execution of the task, each subject had to search by trial and error which of four visual targets (filled disks, upper left, upper right, lower right, and lower left; **Fig. 1A**) simultaneously presented on a video screen was associated with a positive feedback. A trial started with the onset of a white central fixation point 1000ms before the onset of the four grey targets. Subjects were instructed to fixate the fixation point during the entire trial. 1300ms after the target onset presentation, all four targets turned white as a "Go Signal". The subject could then respond by pressing one of four buttons on a response box and within a time limit of 2500ms. Subjects were asked to react as fast as possible to the "Go Signal". At button press, all targets switched off and a delay of 1000ms elapsed before the presentation of a visual feedback lasting 700ms. Feedback

corresponded to a central red or green square for negative and positive outcome, respectively. After each incorrect choice (INC) the subject could continue searching for the correct target. The discovery of the correct target was indicated by the presentation of the first green feedback (CO1), representing the end of the search period and the beginning of the repetition period. During the repetition period, subjects could repeat the correct choice for two trials (COR). A repetition ended with the onset of a central yellow circle, named “Signal-to-Change” (SC), presented 700ms after the feedback offset and for 1000ms. The SC stimulus indicated the end of the current problem, and thus the initiation of a new search for the following problem (see figure 1a). Each block was composed of 28 problems, and all participants made 2 blocks (performed in 2 separate sessions).

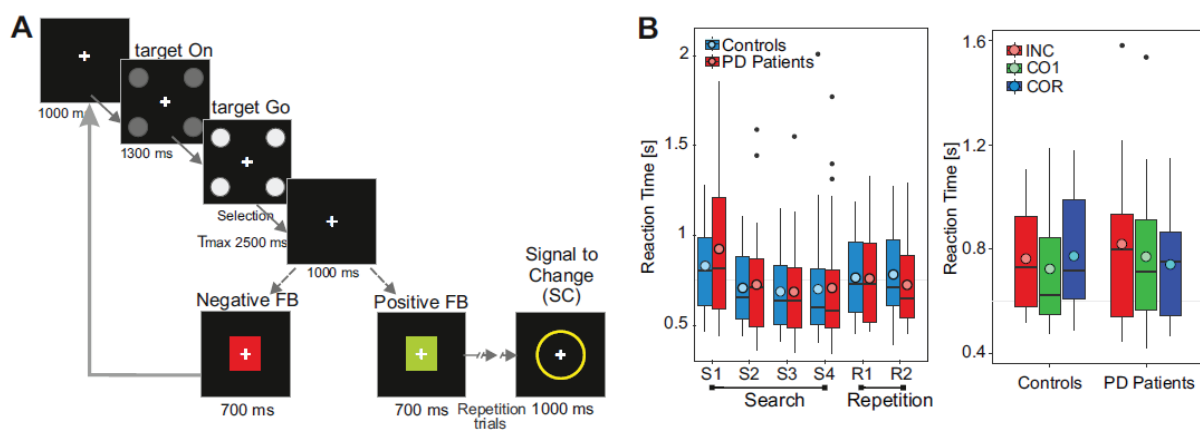


Figure 1. A. Behavioural task. Each trial starts with a fixation point, then the targets appear, showing the options to choose from. Target presentation is a signal to prepare the response. Then a GO signal is presented ("Target Go", targets turn white), and the subject can select a target and touch the corresponding button in less than 2.5 sec. Feedback is delivered for 700ms - positive (green box) or negative (red box). The search period ends when the correct choice is made (1st correct feedback). The repetition then starts, and the subject must select the same option in two more trials before the problem is completed and the signal to change appears indicating the start of a new search period. **B. Left.** Reaction Times PD Patients vs Control. Mean Reaction time box plot of PD patients (red) and controls (blue), the x-axis presents the choice instance, both in search and repetition. The circle represents

the average reaction time per trial and subject group. **Right.** Reaction Times in Control and PD patients by feedback type. Mean Reaction time box plot for Incorrect Feedback (INC, red), first correct feedback (CO1, green) and correct feedback in repetition (COR, blue). The colored disks over boxes represent the mean values.

Behavioral analysis

Performance in the trial and error task was quantified using : the number of unsolved problems, defined as problems where the subject did not complete the search or repetition periods; the number of *Repetition Errors*: correspond to errors committed only in the repetition period; the number of *Search errors* which are divided into: *memory errors*, defined as the selection in the search period of one target that was already selected, but not consecutively, and associated with a negative feedback (for example, the four targets being designated as 1 to 4, a choice sequence with a memory error would be: 3 2 3 1 ...), and *Perseverance errors*, where despite receiving a negative feedback the same option is selected again (e.g. 3 2 2 1) .

Response times (i.e. time between the Go signal and the touch of a button) were analyzed and grouped in trials for the first, second, third and fourth search trials, and for the first and second repetition trials of each problem.

EEG recordings and analyses.

Each experimental recording was preceded by a practice to ensure that subjects (controls and patients) had understood the behavioral task. During task performance the electroencephalogram (EEG) was recorded using a 40 channels NuAmp Express System from 31 active Ag/AgCl electrodes using the standard extended 10-20 system: Fp1, Fp2, F7, F5, F3, Fz, F4, F6, F8, FC3, FCz, FC4, FT8, T3, C3, Cz, C4, T4, TP7, CP3, CPz, CP4, TP8, T5, P3, Pz, P4, T6, O1, Oz and O2. The horizontal EOG was recorded from 2 electrodes at the outer canthi of the eyes, and the vertical EOG was recorded from 2 electrodes above and below the left eye. The 40 monopolar channels NuAmps amplifier was used (Neuroscan Inc.). The forehead was used as ground. EEG and EOG data were sampled at 1000 Hz (Acquire, Neuroscan Inc.) with 0.1 to 100 Hz band-pass filter, and stored continuously on

a PC hard-disk together with stimulus and response markers. Individual Ag/AgCl electrodes were adjusted until the impedance stayed below 5 K Ω .

EEG Pre-processing. Continuous signal analyses were done using Matlab 2014 software (Matlab, The MathWorks Inc. Natick, MA, USA) and the Fieldtrip toolbox (Oostenveld et al., 2011b). All EEG data were segmented in epochs from -1000 to 2000ms centered on the onset of feedback stimulus, with a large window to accommodate edge artifacts induced by wavelet convolution. We removed trials with signal amplitudes superior to 200 μ V. We applied a Butterworth filter with zero phase, between 1 and 60 Hz and a specific filter DFT to remove 50Hz. Eye-blink artifacts were corrected by using SOBI (Second Order Blind Identification). To represent the results, data were segmented between -100 and 600ms centered on feedback onset.

FRN. A baseline correction was applied to all segments, by subtracting the average of the -300 to -100ms window for each trial. The FRN-amplitude was defined as the peak to peak amplitude difference between the negative peak detected in the 250 - 400ms time window and the preceding positive peak detected in the 150 - 300ms window at electrode Fz. Trials were then classified according to feedback type (INC, CO1, COR) and group (control, PD patients) to obtain the average signal.

The number of segments used for EEG analyses for the two groups were, for Parkinson disease patients group: INC, mean=79.6, std=11, min=56, max=96; CO1, mean=54.9 std=3.1, min=45, max=56; COR: mean=110.3 std=5.4, min=91, max=112, and for Control group: INC, mean=84.6 std=10.8, min=64, max=104; CO1, mean=55.3 std=2.3, min=47, max=56; COR, mean=108.9 std=6.6, min=88, max=112.

Time frequency (TF) analyses. Each epoch was convolved with a set of Morlet wavelets, with the following parameters: number of cycles 6, width of Gaussian kernel 3. The frequency band of interest was 3 to 60Hz in 100 logarithmically spaced steps. A baseline correction was applied using the frequency average power from -300 to -100ms. The peak amplitudes of activity of the average resultant matrix for each subject was extracted in 2 windows of interest, theta band: 3 to 7Hz, in the windows 200 to 600ms post-feedback, and beta band: 15 to 30 Hz in the 300 to 600ms window post-feedback. The ROIs for time-frequency analyses were chosen based on our own experience of TF

analyses with human and animal data as well as based on previously used ROIs. Frequency limits are usually around these limits: e.g. 1-8Hz in Lara and Wallis 2014, 3-9 Hz in Babapoor-Farrokhran et al. 2017, 4-8 Hz in Singh et al. 2018 and Narayanan et al 2013 for Theta (Babapoor-Farrokhran et al., 2017; Lara & Wallis, 2014; Narayanan et al., 2013; Singh et al., 2018b). Regarding Beta band limits we chose the 15-30Hz limit to cover low and high beta ranges as several types of beta frequencies have been observed (e.g. see Stoll et al., 2016). We indeed separated in 2 different Beta bands, High (12-20Hz) and low (20-30Hz) in the continuous signal analyses presented in figure 4 (see below).

The time extents of ROIs were chosen according to frequency bands and based on visual inspection of time-frequency diagrams, covering the ensemble of phenomena observed post-feedback. We chose a longer window (200 to 600 ms) for the Theta band and a shorter one for Beta band (300 to 600 ms).

In addition, we performed power spectrum density analyses on the continuous recorded EEG for controls and PD patients. We used the same initial processing methodology as for time-frequency analyses, but taking the first 13 minutes in the task per subject as a continuous signal (13 minutes corresponding to the maximum duration of stable continuous signal, across all subjects), on which we applied a filter between 1 to 60Hz to then obtain the grand average per group, controls and PD patients. Finally cross-frequency correlation matrices were calculated from power spectral density for controls and PD patients (Llinás et al., 1999).

Statistical analyses

All statistical analyses were performed using R (R Development Core Team, 2008). For behavioral analyses, each variable (number of unsolved problems, number of repetition error, number of memory error and number of perseverative error) was fitted using mixed generalized linear models with Poisson distribution with 2 (group: Patient, Control) x 2 (Block number: Block 1, Block 2) design. For response time analyses we performed 6 (Stage: 1st Search, 2nd Search, 3th Search, 4th Search, 1st Repetition, 2nd Repetition) x 2 (group: Patient, Control) x 2 (Block number: Block 1, Block 2) repeated-measures ANOVAs. The reaction time measured in trials with different feedback types were analyzed using a 3 (Feedback: INC, CO1, COR) x 2 (group: Patient, Control) repeated-

measures ANOVA. For the FRN amplitude analyses we performed 3 (Feedback: INC, CO1, COR) x 2 (group: Patient, Control) repeated-measures ANOVA. The effect of condition (Control vs Patient) was directly evaluated with 1-way ANOVAs.

In time-frequency analyses, measures were tested against baseline values through 1-way ANOVAs for PD patients and controls for the 3 feedback types. The direct contrast between measures in Controls and Parkinson groups was also tested independently for each feedback. In both cases multiple measures were accounted for by using FDR correction.

Statistical analyses were carried out with a significance threshold of $p = 0.05$. Sphericity was tested prior to running repeated measures ANOVA using a Mauchly's test of sphericity. The Greenhouse-Geisser epsilon was used to correct for possible violation of the sphericity assumption. We report p-value after the correction.

RESULTS

Behavior

Results were obtained after the analysis of 15 control subjects in 30 recording sessions and 17 PD patients in 34 recording sessions. PD patients performed significantly more unresolved problems (mixed Poisson glm, group effect: Deviance(1,62) = 54.7, $p = 0.0055$) and repetition errors (group effect: Dev (1,62) = 131.9, $p = 4.11e-5$) than controls, but the number of memory errors were not significantly different between subject groups, and did not vary between blocks. The frequency of perseverance error differed between group and increased in the second block of the session (Poisson glm, Group x Block interaction, Dev (1,60) = 128.5, $p = 0.024$).

To study RTs of PD patients and control subjects we focused on search and repetition trials from correctly solved problems. We sorted trials according to their rank in the problem (First to fourth trials in the search periods and first and second in the repetition periods). This provides a view of the average dynamic of RTs during a problem (**Fig. 1B**). RTs were not different between groups (PD patients and control subjects) or between

blocks (1st versus 2nd block). For both groups, RTs were longer in the first search trial and decreased over the search period (mixed glm, group x block x trail-rank, $F(5,330)=14.07$, $p < .0001$).

Feedback-related negativity

The feedback-related potential is modulated by feedback valence and outcome expectancies (Cohen et al., 2007; Sallet et al., 2013). Because its modulation might depend on the dopaminergic system, we looked for changes between controls and PD patients. The electrophysiological responses for the different types of feedback (negative feedback: INC, first positive feedback: CO1 and positive feedback in repetitions: COR) for control and PD patients at electrode Fz are shown in **Fig. 2A**. The distributions of individual FRN peak amplitude (negative – positive peak, see methods) per group are shown in **Fig. 2B**. We found no interaction between feedback type (INC, CO1, COR) and group (control, PD patient) (type x group, $F(2,60) = 0.62$, $p = 0.54$), but a main effect of feedback type (type, $F(2,60) = 34.7$, $p < .0001$) on the FRN (**Fig. 2B**). On the Scalp topography, for both groups and the three types of feedback, the negative frontal negativity is clearly observed in control subjects for INC and CO1 (**Fig. 2C**). An analysis across midline electrodes showed an effect of electrode on the difference of amplitude between INC and COR and between CO1 and COR, but no effect of group (ANOVA, electrode x group, CO1-COR: electrode $F=4.86$, $p<0.01$, group $F=3.4$, $p=0.06$, interaction: ns; INC-COR: electrode $F=5.53$, $P<0.001$, group $F=2.58$, $p0.1$, interaction: ns). In controls, the FRN observed in response to feedback at Fz in INC and CO1 trials was larger than in COR trials. PD patients only the FRN at CO1 mean amplitude differed from COR (Tukey Post-hoc statistics, Bonferroni adjusted, Control_COR vs Control_CO1: Estimate= -2.94, Std Error=0.52, z-value= -5.66, p-value=2.3e-7; Control_COR vs Control_INC: Estimate=-1.93, Std Error=0.52, z-value=3.71, p-value=0.003 ; PD_COR vs PD_CO1: Estimate=-2.99, Std Error=0.49, z-value=-6.12, p-value=1.44e-8). However, directly contrasting FRN measures for the different feedback types in Controls vs. Patients revealed that FRN measures were not impacted by condition: INC $F(1,30) = 1.31$, $p=0.26$; CO1: $F(1,30) = 0.1$, $p = 0.76$ and COR: $F(1,30) = 0.25$, $p = 0.62$. Thus, the amplitude and pattern of FRNs was present in the PD group of subjects like in Controls.

Feedback-related oscillations and power spectrum analyses

Neurophysiological markers of feedback processing have been observed consistently at the level of theta and beta oscillations for frontal midline electrodes (M. X. Cohen et al., 2007b; Doñamayor et al., 2011a; HajiHosseini et al., 2012a; HajiHosseini & Holroyd, 2015; Marco-Pallares et al., 2008a; Marco-Pallarés et al., 2009; van de Vijver et al., 2011a). Because such markers are potentially influenced by the systems altered in Parkinson's disease we also looked for modulations of feedback-related oscillations depending on feedback types and subject groups. Feedback-related activity was thus also studied in the frequency domain.

Time-frequency diagrams revealed differential increases of theta and beta oscillations at the time of feedback for all types of feedback. **Figure 3** shows the significant post-feedback changes in power from baseline for each group of subjects and each feedback type (**Fig. 3A, top**), as well as subject group difference (**Fig. 3A, bottom**). It also shows an analysis focused on specific time windows for theta and beta bands (see methods. **Fig. 3B**). The window analysis showed that theta activity was sensitive to feedback type only (Main effect feedback_type x group: group, $F(2,60) = 0.22$, $p = 0.80$, ns; feedback_type, $F(2,60) = 11$, $p = 0.001$). Also, for both groups of subjects, feedback-related theta in the first correct trial was greater than in correct trials during repetitions as for the FRN (Post-hoc Tukey contrasts: $COR_{Control} - CO1_{Control}$: Std = -336.3, Error = 94.5, z value = -3.6, $p = 0.005$; $COR_{PD} - CO1_{PD}$: Std = -253.9, Error = 88.7, z value = -2.9, $p = 0.046$). Theta for INC differed only marginally from theta in COR trials ($F(248.5,94.5) = 2.63$, $p = 0.086$). The refined time-frequency analyses confirmed the absence of subject group effect on post-feedback Theta power (**Fig. 3A, bottom**).

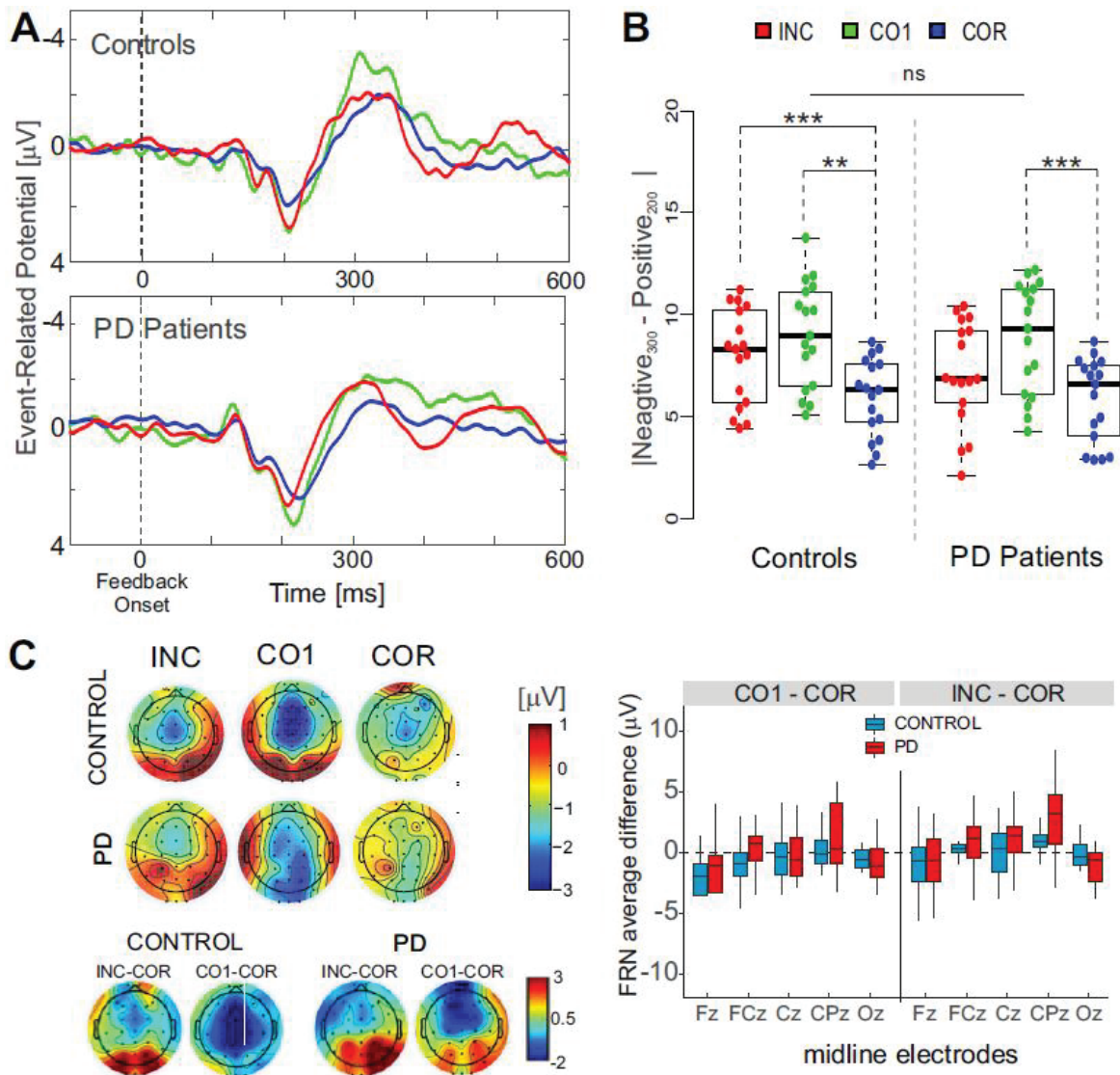


Figure 2. A. Grand-average electrophysiological feedback responses for INC, CO1 and COR trials in controls subjects and PD patients at electrode Fz. ERP are shown for incorrect response (INC, in red), first correct response (CO1, in green), correct response in repetition (COR, in blue), and are aligned on feedback onset. **B.** FRN amplitude. Distribution of differences between the negative peak and preceding positive peak per subject (point) for controls and PD patients in response to 3 different feedback types. Stars indicate significance of post-hoc Tukey statistical comparisons ($\sim p < 0.1$, $* p < 0.05$, $** p < 0.01$, $*** p < 0.001$). **C.** Scalp topography for each feedback type, centered on the time of the main negative peak (FRN), and for differences with COR FRN (bottom row). On the right, boxplots show the difference between FRN values measured at CO1 and COR and between INC and COR, by groups of subjects and displayed for the midline electrodes.

In contrast to theta, feedback-related beta power seemed mostly present for control subjects. In the beta range (20 to 30 Hz between 300 to 600ms) the maximum power was significantly altered by feedback type (Main effect feedback type, $F(2,60) = 7.46$, $p = 0.001$), and by subject group (Main effect Group, $F(1,30) = 7.48$, $p = 0.01$) (**Fig. 3B**). The interaction feedback-type x subject group was marginal (Beta: feedback type x Group, $F(2,60) = 2.87$, $p = 0.064$). Further post-hoc analyses showed that increased beta power was indeed observed only in response to CO1 feedback in control subjects, and differed significantly between INC and COR feedback, and compared to CO1 in PD patients (Post-hoc, Tukey Contrast: $COR_{Control} - CO1_{Control}$: Std = -106.17, Error = 26.56, z value = -4, $p < 0.001$; $INC_{Control} - CO1_{Control}$: Std = -89.73, error = 26.56, z value = -3.4, $p = 0.009$; $CO1_{PD} - CO1_{Control}$: Std = -122, error = 34.67, z value = -3.5, $p = 0.005$; **Fig. 3B**). Note that since feedback-related changes in power are estimated with reference to pre-feedback power, the results in PD patients (and loss of variance as shown on figure 3B) revealed a complete lack of change in beta power. Contrasting time-frequency decompositions showed between-group effect in the beta range predominantly for CO1 feedback (**Fig. 3A, bottom**). In conclusion, a main effect of group (health condition) was observed for a beta power increase at the time of positive feedback, in particular the 1st positive feedback of problems.

Spectral changes

Because of the lack of post-feedback beta power increase in patients, we assessed whether more global changes in oscillatory activity could be observed. To do so, instead of focusing on event triggered EEG we analyzed the frequency composition of the 13 first minutes of signal recorded in the session of each subject (including task performance). We focused on the 1 to 60Hz range, and looked in particular within the beta band separating 12-20Hz and 20-30Hz sub-bands. The PSD for one subject stood as an outlier in the analyses and was removed from the group. The average power spectrum clearly revealed the drop in Beta for patients compared to controls, which was not present for theta or alpha bands (One way ANOVAs, Theta (4-8Hz): $F(1, 30) = 0.11$, p -value=0.74; Alpha (8-12Hz): $F(1, 30) = 0.12$, p -value= 0.73; Low Beta (12 - 20Hz): $F(1, 30) = 4.87$, p -value=0.035; High Beta (20-30Hz): $F(1, 30) = 7.820$, p -value= 0.009; **Fig. 4A**). Neither low nor high beta powers correlated with the individual clinical test scores (Pearson

correlations, for PD patients: Low Beta vs DDEL $r=0.11$, $p=0.68$; PD: High Beta vs DDEL $r=0.06$, $p=0.84$).

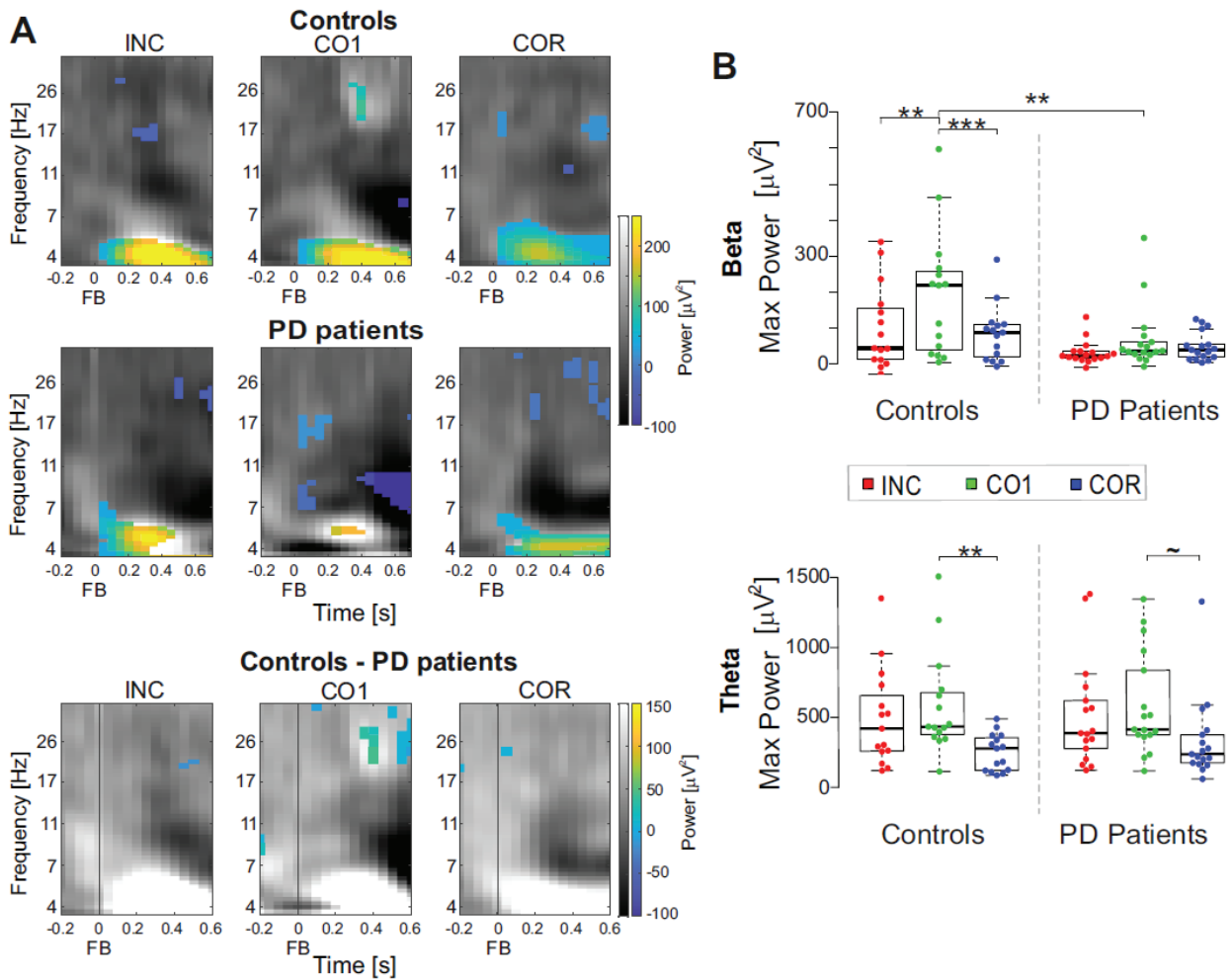


Figure 3. A. Time frequency plots for each feedback type for patients and controls computed for signal recorded at Fz. Top rows. In gray scale the normalized time-frequency plot between minimum (black) and maximum (white), while on the color scale, the power values significantly different from the baseline (-300 to -100 ms prior to feedback), obtained through 1-way ANOVA with FDR correction ($p < 0.05$). Note how theta activity in PD patients loses significant difference evoked by the appearance of feedback compared to baseline, especially in response to the first positive feedback, CO1. **Bottom row.** Time-frequency difference graph of controls minus PD patients for the 3 types of feedback. In gray scale the normalized difference between minimum (black) and maximum (white), while in colors the

significant difference between Controls and EP Patients using 1-way ANOVA with FDR correction. Only the beta activity around of 400ms reveals an effect given by the condition (control or PD patient). B. Peak-Amplitude distributions per feedback type and group (control, patient) for beta (15 to 30Hz across 300 to 600 ms post feedback) and theta (3 to 7 Hz, across 200 to 600 ms post feedback) bands. Stars indicate significance of post-hoc Tukey statistical comparisons ($\sim p < 0.1$, $ p < 0.05$, $** p < 0.01$, $*** p < 0.001$).*

As altered cross-frequency correlations have been observed previously in different pathologies (Llinás et al., 1999), suggesting abnormal organization of brain dynamics induced or correlating with pathological conditions, we performed cross-frequency correlations maps specifically for signal captured by electrodes C3 and FZ. The analysis of the continuous EEG over the period of 13 min revealed differences of the cross-frequency correlation pattern in PD patients compared to controls. PD patients showed a lower level of cross-correlation in particular between beta and gamma bands (**Fig. 4B**). The drop in cross correlation is particularly visible on the C3 electrodes, C3 putatively capturing signals from above motor cortex on the contralateral side of the hand used by subjects (Right hand).

DISCUSSION

We assessed the neuropsychological status, behavioral performance, and EEG markers of performance monitoring functions using a trial-and-error task in recently diagnosed PD patients, compared to healthy controls.

In our study, PD patients presented significantly higher levels of apathy, but not depression, and more cognitive deficits than the control group as evaluated by standard clinical tests. This pattern of neuropsychological impairments in PD patients at early stages of the disease is in accordance with recent studies that encourage a global approach in the research and treatment of Parkinson's disease, which include the classical motor symptoms but also the non-motor symptoms impacting the cognitive and

emotional domains (Aarsland et al., 2009; Foltynie et al., 2004; Kaji & Hirata, 2011; Olanow & Obeso, 2012a). At present medical management of PD patients is principally focused on dopaminergic substitution, and neuropsychiatric impairments are frequently underestimated.

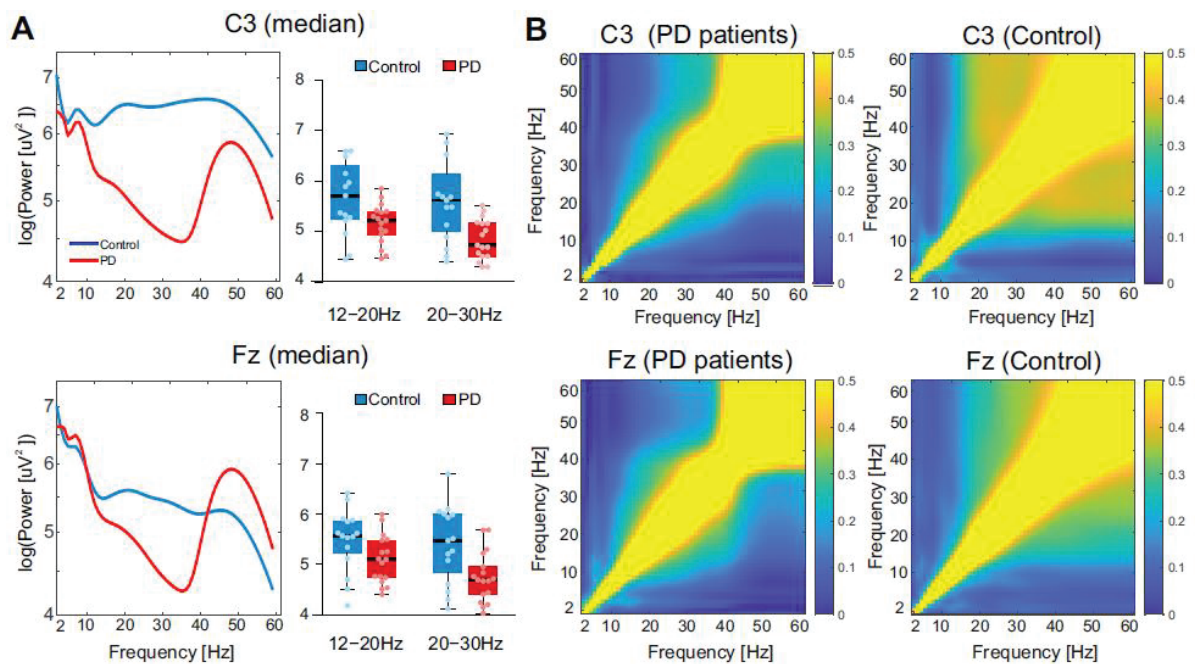


Figure 4. Power spectrum over Fz and C3 in the first minutes of recordings. A. On the right, power spectral density of continuous EEG over a period of 13 min for control (blue) and PD patient (red) for signal at electrode C3 (top) and Fz (bottom). On the left, measures for 2 Beta sub-bands for both groups. **B.** Correlation matrices of power spectra of continuous EEG for control (left) and PD patients (right).

The global performance of PD patients in the experimental trial-and-error task was qualitatively similar to that of controls. Patients could understand the task and finished a majority of problems during a session. They nevertheless failed to terminate problems in more cases than controls, and committed more perseverative errors during the repetition period than controls. Such results might be connected to those suggesting executive types of dysfunction in PD especially when subjects are engaged in cognitive tasks

requiring active adaptation of decisions and problem solving as measured for instance using the Raven matrices (Brück et al., 2004; Nagano-Saito et al., 2005). RTs were similar in PD patients and controls with higher RTs in search than in the repetition, a pattern that is typically seen in such tasks and that suggest the underlying structure of cognitive progression during problems was not altered in the PD group.

Feedback-related potentials and oscillations in PD patients

Studying the FRN can provide important clues about the nature of the neural mechanisms contributing to error processing, decision making, and reinforcement learning, both in healthy subjects and patients with alterations of various relevant brain systems as e.g. the dopaminergic system in Parkinson's disease. One of the aims of this study was to determine if the FRN, modulated by the valence of performance feedback would be impacted in a selective manner by Parkinson's disease. During the trial and error learning protocol the FRN in control subjects reflected the evaluation of both negative and positive feedbacks when those are relevant for adaptation (i.e. in incorrect trials and for the first positive feedback). An FRN signal at Fz and FCz was elicited by negative feedback during search and to the first reward in a problem. The FRN was reduced for positive feedback during repetition. Our objective was to test whether the early effects of neurodegenerative disease would reveal changes in FRP and possibly for different feedback types (positive versus negative, informative (INC, CO1) versus non-informative (COR). Feedback type effects were not changed in PD patients compared to controls. It somewhat contrasts with a recent study showing that a fronto-central positivity to positive Feedback was diminished in early diagnosed PD patients compared to controls in a probabilistic two alternative forced choice task, but the FRN for negative outcomes (no reward) did not vary between subject groups (Brown et al., 2020). In fact, a differential effect of probability of reward on positive and negative feedback-related potential has been observed in healthy subjects (M. X. Cohen et al., 2007b).

In the current study we hypothesized that the FRN signal could be altered for the PD patient group after informative feedbacks in particular and potentially differently for positive and negative feedback, which would have been in line with some studies evaluating the ERN in Parkinson's patients (Willemsen et al., 2009b). The same effect

was found for post-negative feedback Theta power increase which also reflects feedback processing (Cavanagh et al 2010 Neuroimage) and has been found altered in Parkinson's disease patients (Singh et al., 2018b). We did not find any significant difference as in some previous studies (e.g. Holroyd et al 2002). The limitations of our study that might explain such negative results are detailed below.

Parkinson's disease and task-related oscillations

In controls, theta power and beta power increase were elicited by feedback in search, showing in particular higher increases for the first correct feedback (CO1) compared to positive feedback in repetition. In the context of executive functions and adaptive behavior, theta activity (4 - 8 Hz) has been detected on the frontal midline in response to negative feedback during gambling and learning tasks (M. X. Cohen et al., 2007b; De Pascalis et al., 2010b; Marco-Pallares et al., 2008a), with modulations similar to those for the FRN (Chase et al., 2011; Cunillera et al., 2012a; Leicht et al., 2013). Other studies also showed changes of low-frequency activity in response to positive feedback (Doñamayor et al., 2011a; HajiHosseini et al., 2012a). Moreover, activity at higher frequencies including the beta range between 20 to 30Hz, with a similar frontal midline origin to the theta oscillation, have been described in response to positive feedback (M. X. Cohen et al., 2007b; Doñamayor et al., 2011a; HajiHosseini et al., 2012a; HajiHosseini & Holroyd, 2015; Marco-Pallares et al., 2008a; Marco-Pallarés et al., 2009; van de Vijver et al., 2011a). Cunillera et al. 2012, using a modified version of the Wisconsin Card Sorting Task that includes exploration and exploitation phases comparable to our protocol, reported increased beta activity at the first correct feedback of a series and not during the repetition (Cunillera et al., 2012a). Other studies have reported beta activity for negative feedback (M. X. Cohen et al., 2008; van de Vijver et al., 2011a), or, using magnetoencephalography (MEG) after reward delivery (Doñamayor et al., 2011a).

In Parkinson's disease patients, when compared to the control group, mid-frontal theta activity was not different at the time of feedback compared to other feedback types. Previous reports observed a global change but no differential change in error-related ERP and theta power between error and correct responses in Parkinson's patients compared to controls (Singh et al., 2018b). We found however that post-feedback beta power

changes were altered in the PD group especially for positive feedback-related activity in search compared to repetition. Further analyses revealed that beta oscillations were altered (reduced) more broadly, inducing a drop in cross-frequency dynamics involving beta and gamma regimes of oscillations. This result suggests that while feedback-related beta is altered it is unlikely that it reflects a deficit touching selective mechanisms (e.g. feedback-related) but maybe more a global alteration of task-relevant beta power. Abnormal beta oscillations in PD patients have been widely documented (Jackson et al., 2019; Jenkinson & Brown, 2011). Studies have observed an abnormal increase in subcortical beta power as well as in scalp electroencephalography recordings, especially in rest condition (Babiloni et al., 2017; Jackson et al., 2019). In fact, variations of beta power in PD patients are contextually dependant on dopaminergic medication. Studies showed that in the off medication state, EEG inter-electrode coherence in beta frequency increased in PD patients during rest, and the onset of dopaminergic medication reduced it (George et al., 2013). However, during a cognitive task in On-medication state, frontal beta power increased compared to Off-medication, showing that medication reduces abnormal resting beta activity but increases task-relevant beta activity (George et al., 2013). This is in line with reports of reduced anticipatory beta oscillations in rhythmic auditory task, that were recovered with levodopa or STN-DBS while STN-DBS reduced the resting increase in beta oscillation power (Gulberti et al., 2015). In our study, it is likely that the reduced beta power and cross frequency synchrony in the first 13 minutes of task performance was due to such task-related alteration of beta oscillations.

Finally, in a monkey model of Parkinson's disease, frontal beta power changes have been tracked and partially reflected reduced engagement in the trial and error task induced by a progressive dopaminergic system lesion (C. R. Wilson et al., 2016). In the present study, PD patients showed on average significantly worse scores on the apathy scale, but those scores did not correlate with the beta power measured during the first minutes of EEG recordings. Further studies focused on the motivational aspects of the disease and neural markers are required.

LIMITATIONS

This study described feedback-related EEG signals in Parkinson's patients and healthy controls in a deterministic trial and error learning task allowing analyses over several feedback types. Whereas the study allowed for between-groups comparisons the small sample size in each group must be noted as a limitation for this study. Yet several relevant features of feedback related potentials as well as of feedback-related oscillation power have been observed for both groups and in accordance with past studies. We do not find significant differences in FRN amplitude or theta power between PD patients and controls, but again sample size might have been a limitation. Several studies have also compared FRN and oscillations in PD patients ON versus OFF medication seeking a particular effect of dopaminergic transmission on performance monitoring signals. Unfortunately, the testing conditions for patients at the time and place of the study prevented us to perform such within-subject comparison. Previous studies have observed no effect of medication (OFF vs ON) on error- or feedback-related markers (Singh et al. 2018, Brown et al. 2020, Stemmer et al. 2007) or a decrease of response-related signals under medication compared to control, with no effect of valence (Seer et al., 2017).

CONCLUSIONS

This study shows that some markers of performance monitoring, specifically Beta oscillations, are selectively altered in the early stages of Parkinson's disease, yet those markers are accompanied by global changes in beta oscillation. Whereas such effects on neurophysiological markers could be relevant for the characterization of the early stages of Parkinson's it must be noted that these do not correlate with clear behavioral markers or with scores established by clinical tests.

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4.2. Human frontal neural dynamics reflect strategies for performance monitoring and decisions to check

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ABSTRACT

Exploration and information seeking contribute to efficient adaptations in novel, changing and unpredictable environments. The decisions to explore are associated with specific activity in subregions of the frontal cortex which, in animal recordings, revealed dynamics specific to this type of decision. The present work adapted a protocol designed to stimulate voluntary decisions to check information in non-human primates, to carry out a study in humans using electroencephalography techniques, in order to identify markers of exploratory and adaptive functions. Behavioral analyses revealed dissociations between different subject groups based on information seeking strategies, potentially related to the type of information gathered after checking decisions or to the specific motivations leading to such decisions. Analyses of the power spectrum density and phase synchrony between frontal electrodes reflected dynamics associated with checking decisions. This study shows that human neural dynamics within the frontal lobe can reflect information seeking decisions and strategies.

INTRODUCTION

Uncertainty drives exploration of the world, as a positive or negative incentive for voluntary behaviours. In turn, one natural consequence of exploration and information seeking is the reduction of uncertainty, forming a time extended adaptive cycle devoted to converge towards more comfortable, more rewarding and/or less anxiogenic situations. The temporal extension of such behaviours is a complex process as it entails mechanisms for continuous information integration during the course of exploration and also for the updating of motivations and persistence to pursue such behaviour (Kolling et al., 2016). While monitoring of uncertainty is a fundamental aspect of normal cognition, it could also be one key to understand abnormal decisions in psychiatric diseases (Uddin, 2021). Indeed, ill-managed uncertainty drives anxiety, abnormal checking and verification, or other uncontrolled behaviours (Maia & Frank, 2011).

Making decisions in certain established states versus to quit such state and explore alternative entails different computational and neural mechanisms (Domenech & Koehlin, 2015; Kolling & O'Reilly, 2018). Past work has shown that evaluative functions for exploratory decisions involve the midcingulate cortex (MCC) and interactions with lateral prefrontal areas (LPFC) (Cavanagh & Frank, 2014; Johnston et al., 2007; Khamassi et al., 2015; Rothé et al., 2011; Stoll, Fontanier, et al., 2016; Womelsdorf et al., 2014). MCC - LPFC interactions are thought to contribute to the monitoring and evaluation of behaviourally relevant feedback and to trigger specific adaptive decisions or strategies, including exploratory choices, and to contribute to the building or use of prospective values to guide sequential behaviours (Cavanagh & Frank, 2014; Khamassi et al., 2015; Kolling et al., 2018)

The respective contributions and synergy within networks formed by frontal areas remain to be clearly defined. Neurophysiological recordings in monkey frontal cortex have shown that MCC neural activity codes for feedback information during adaptation (after negative performance feedback for instance) but also showed that very similar MCC neurons encode self-initiated information seeking decisions (Stoll, Fontanier, et al., 2016). This revealed a functional overlap, within MCC, between the neural substrate for feedback processing and the substrate of codes for decisions to explore. In fact, one could

also decode, from MCC neural activity, the information used by the animal to regulate decisions over long timescales, i.e. across multiple trials while monitoring for performance was also proceeding. Such data suggest that neural markers in medial frontal areas can reveal the temporally extended process of adaptation.

Medial frontal regions might serve as regulators for cognitive control functions, i.e. selection of actions and plans in reaction to changing performance or when decisions to switch to novel or uncertain environments are made (Burle et al., 2005; Domenech et al., 2020; Domenech & Koechlin, 2015; Kolling & O'Reilly, 2018; Shenhav et al., 2013; Vidal et al., 2020). Such functions are crucial to adapt and organize behaviour in time, based on adapted and flexible strategies. In monkeys, recordings have suggested that MCC contribution to self-initiated decisions (and feedback processing) preceded LPFC activity, while the reverse was observed for decisions guided by memorised visuospatial information (Stoll, Fontanier, et al., 2016). This suggests that the dynamics of MCC-LPFC interaction is context-dependant and might indeed dissociate within-state versus state - change decisions making (Kolling & O'Reilly, 2018).

Here we tested whether neural markers of performance monitoring and exploratory decisions observed in human EEG signals would reveal the contribution of performance monitoring signals to strategically organized exploratory decisions, and whether medial to lateral frontal interactions played differential roles in various types of decisions. EEG provides the temporal properties adequate to study the combination of physiological mechanisms occurring at different temporal scales in humans. We adapted a Check-or-Play task developed in a previous monkey study by Stoll et al (2016) for use in human experiment.

We show that groups of humans develop different strategies to regulate checking decisions in this task based on information gathered voluntarily. Event-related potentials and power spectrum densities over frontal sites revealed that both performance monitoring and the differential strategical use of information can be extracted from frontal neural dynamics.

METHODS

Participants

35 right-handed healthy volunteers (22 females, 13 males, mean age 25 ± 4 years) with no history of neurological or psychiatric disturbance participated in the study. 5 subjects were excluded from the study by EEG recording with low SNR (signal to noise ratio) and another 3 subjects due to low performance in the task (under 70% of full gauge obtained). 27 subjects with valid data for the study were included for the study (16 females, 11 males, mean age 26 ± 4.9 years).

During the experiment subjects were sitting in a chair in front of a video screen and a computer keyboard placed on a desk (at 65cm from the screen). Subjects' responses were recorded through the keyboard using the arrow keys.

Study Design

The behavioural protocol was an adaptation of Stoll et al 2016 (Fig. 1A). The task was presented to subjects as a series of 'Play' trials in which they could gain points. They could also win a bonus of points after a certain number of accumulated points. By using a Check option, they could observe how close they were to have access to the bonus, and they could gather the bonus by using the same check option. In order to motivate subjects a score was computed and displayed at the end of each block of trials.

In each trial a subject was first facing the choice between 2 visual items representing 2 'levers' to select either the Play or the Check options, respectively a titled bar displayed on the left, or a green circle displayed on the right. By selecting the Play option, a subject initiated a trial of a visual discrimination task, named the 'Main' task. A white bar, the cue stimulus, with one of 8 possible tilts was presented for 500ms. The tilt was 0 to 5 degrees with logarithmic separation leading to 8 different orientations. A fixation point then appeared for 1.5 to 2.5 seconds, after which two bars (the targets) appeared, one tilted 45 degree to the right and the other 45 toward the left (see figure 1.A). The two stimuli were displayed one on the left and one on the right of the fixation point, depending on 2 conditions: congruent (rightward tilted bar on the right) or incongruent (rightward tilted

bar on the left of the fixation point). The onset of these targets signalled the possibility to respond. Subjects had to respond within 2 seconds using the left and right arrow keys to select the bar tilted in the same direction as the cue. A correct response was followed by the onset of a feedback for 1 second: a green square with a “+1” presented on its centre and indicating a one-point gain. After an incorrect response, a negative feedback (red square with an indication “+0”), was presented for 1 second.

By selecting the Check option, the subject triggered the onset of a gauge stimulus, i.e. a green disk with a diameter reflecting the proximity to a full gauge (represented by a large green circle). The gauge had 7 different levels. The number of correct responses (also named Speed) required to reach the full gauge varied between blocks and was either 7, 14, 21 or 28. This was pseudo-randomly determined and unknown to the subject. The speed of increase of the gauge thus varied from one block to the next, and checking the gauge size during the block was the only way to learn about its speed.

The final significance of the gauge element for the subject was the possibility to either receive a bonus reward or to avoid a reward penalty when the gauge is full. If the subject checked at full gauge, or after one correct trial after the full gauge was reached, the outcome was revealed to the subject. In the “Bonus” version, the subject earned 25 points (visualized with a green circle with +25), otherwise the problem would end without additional score. On the contrary, in the “Penalty” version, the subject would avoid a penalty of 25 points in her score that would otherwise be delivered if the full gauge was not checked (visualized with a red circle with -25). Whatever the action, the problem ends with the display of a yellow circle.

A session consisted of 4 runs that included the Bonus and Penalty versions. Each run has a time limit of 15 minutes to complete the maximum number of possible problems and to maximize the point gain. The objective of the task is to obtain the maximum possible score. To motivate the participants, at the end of each problem a ranking is shown with the highest historical scores compared to the current score of that participant.

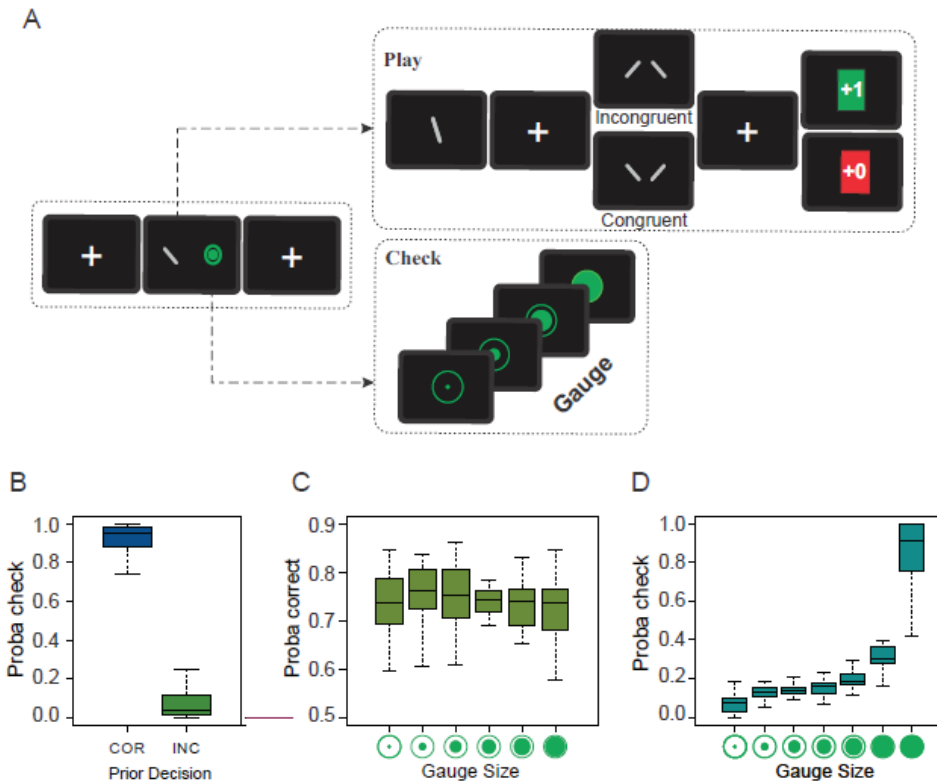


Figure 1. Experimental protocol and general behaviour. *A.* In each trial, the subject is free to decide between Play in the visual discrimination task, where if the subject answers correctly he will win a point, or Check the gauge size, which is a green disk that increases in size based on the points earned in the Play task, across 7 possible dimensions. The speed of increase depends on the number of points necessary to finish the problem (7, 14, 21 and 28 points). If the subject chooses to check at the moment of obtaining the required score, she sees the full gauge and will either earn a bonus or evade a penalty of 25 points. *B.* The subject chooses Check mainly after correct responses (COR) in the Cued Decision. *C.* The probability of obtaining a correct answer in Cue discrimination was not affected by gauge size. *D.* Subjects increased their check frequency as the gauge size increased, showing adaptive checking behaviour.

EEG Recording

The EEG was recorded with 64 active electrodes mounted on an elastic cap (ActiCaps, Brain Products, Munich, Germany). Electrode impedances were always kept below 5 k Ω . The EEG recording was acquired using the Brain Vision Recorder Software Version 1.10 (Brain Products, Munich, Germany). Data were collected with a sampling rate of 2048 samples per second.

The data kept for analyses were those for which subject gained at least 70% of the possible full gauges across the 4 runs.

Data Pre-processing

Data were pre-processed in MATLAB 2017b (Matlab, The MathWorks Inc. Natick, MA, USA) using custom scripts and the Fieldtrip toolbox (Oostenveld et al., 2011). All EEG data were segmented in epochs from -3000 to 3000ms centred on the onset of fixation point at beginning of each trial, with a large window to accommodate edge artefacts induced by wavelet convolution. We removed trials with signal amplitudes superior to 100 μ V and noisy electrodes. We applied a windowed sinc FIR filter with zero phase forward and reverse filter, between 0.1 and 100 Hz, as well as a specific DFT filter to remove 50Hz. Eye-blink artefacts were corrected by using SOBI (Second Order Blind Identification). All channels were re-referenced using the average of the electrodes (not considering eliminated electrodes) and then the removed channels were interpolated. ERPs were transformed into reference-free current source density (CSD) waveforms by computing a second spatial derivative by spherical spline interpolation (order of splines: 4; approximation parameter lambda: 1.0e-005, head radius: 10cm).

Analyses were performed using the following number of trials and segments, first for analyses across all subjects (Mean +/- std): Check = 101.1 +/- 23.6, Play = 419.4 +/- 27.4, Positive Feedback = 308.1 +/- 18.8, Negative Feedback = 110.6 +/- 22.4. For analyses on subgroups of subjects (see behavioural analyses for subgroup definitions): Integrative (Mean +/- std): Check = 96.3 +/- 16.4, Play = 421.4 +/- 28.6, Positive Feedback = 313 +/- 20, Negative Feedback = 107.4 +/- 17 and for the Ballistic group (Mean +/- std): Check = 101

+/- 28.2, Play = 419.8 +/- 29.7, Positive Feedback = 303.4 +/- 19.7, Negative Feedback = 115.6 +/- 27.9.

Event Related Potentials

A Butterworth low-pass filter was applied with a cut-off frequency of 40Hz, and a baseline correction was applied to all segments by subtracting the average signal computed over the window -300 to -100ms before feedback for each trial. The average of the CSD signal was calculated by window of 150ms and shifting by 50ms between -300 and 3300ms centred on the FB onset for the frontal, central and centro-parietal electrodes.

For each bin through all the trials and for each electrode, we fitted a linear mixed-effects model using the following model:

$$\text{Bin}(ch,t) \sim \text{poly}(\text{Gauge Size}^2 + \text{Decision} + \text{Performance} + (1|\text{Subj}))$$

where $\text{Bin}(ch,t)$ is the mean CSD for channel ch and time window t , and $(1|\text{Subj})$ indicate that subject identity was considered as a random effect factor in the mixed-effects model. In this model the Gauge size (values 1 to 7) was fitted with a quadratic function, using the $\text{poly}()$ function in R that performs orthogonal linear and quadratic fits to test for a quadratic influence of Gauge size, an hypothesis driven by the checking strategies of subjects (see behavioural results). Decision denotes the choice [Check, Play] made at the end of the interval. Performance denotes the outcome of the preceding Play trial [INC, COR]. Statistical models were fitted using R (R Development Core Team, 2008). An FDR correction was applied on p-value obtained across bins.

Frequency Analyses

We computed time–frequency decompositions over CSD signal using a complex Morlet's wavelet transform with width of 10, from 4 to 45Hz. To analyse the PSD (power spectral density), three time-windows were defined on each segment centred on feedback onset: a post-feedback window from 0 to +1s, a fixation window (onset of fixation point) from +1 to +2s, and a decision window from +2 to +3s which just precedes the onset of the Play and Check options. We applied a linear mixed-effect model similar

to the one used for ERP segments (described above) on the PSD value per each channel and frequency.

Phase Synchrony

We calculated phase synchrony using the phase-locking value (PLV) computed between pairs of electrodes (Lachaux et al., 1999) using the complex data of wavelet convolution across trials and for each subject. Then a z-score was computed to normalize the PLV signal. A Wilcoxon test was applied across subjects with FDR correction to evaluate the difference in phase locking between Check and Play after positive feedback (Play choices after negative feedback will not be considered in this analysis).

One specific aim was to compare potential synchrony observed prior to the Check vs. Play choice, with synchrony observed prior to the Left vs. Right choice in the main task. Because the time between the stimulus offset and the target onset was variable (between 1.5 and 2.5s with a mean of 2s), we studied the signal using 2 different time-windows: one from -0.3s to +1.9s around the stimulus onset, and a second time-window from -1.3s to +0.3s around the target onset. A Wilcoxon test was applied at each time bin, to test across subjects, the differences between Left and Right responses.

RESULTS

Multiple strategies regulate decisions to check.

Subject chose to play in the main task on 81.3% of trials, with a stable mean performance of 73.5% correct answers. They decided to check on the remaining 18.7% of trials. The decision to check followed a correct answer to the cued decision task on 92.4% of occasions, showing that the check decision is conditioned by performance in the main task (logistic regression: Previous Feedback, Estimate 1.72, Std Error = 0.08, z value = 21.18, p-value < 2e-16) (**Fig. 1B**). The Check frequency increased based on the progress of the task within a block, which implies that the larger the gauge size, the greater the probability that the participants chose to check (Kruskall-Wallis (KW) test; Chi squared = 142.55, df = 6, p-value < 2.2e-16) (**Fig. 1D**). The performance in the main task was not

affected by gauge size (**Fig. 1C**). We observed no behavioural change in these measures between the versions of the task (Bonus, Penalty), and this parameter will not be considered further.

The gauge size provides relevant task information and the subjects generated different strategies based on this information. We analysed how the gauge size seen after a decision to check affected the future decision of when to perform the next check, by measuring the number of correct trials made in the Main task between checks. The subjects showed differing strategies in their management of when to next check. To evaluate the effect of the observed gauge size (information gathered by checking the gauge) on the checking strategy, we calculated the average 'distance' (in terms of correct trials) between a check n and the next check ($n+1$) for each gauge size observed after check n . Previous results in monkeys during the original version of this task, showed that as the gauge size increased, the distance to next check in number of correct answers decreased linearly (Stoll, 2016). The function describing the relationship between distance to check and gauge size observed reflect the strategy implemented by the subject to use the information provided by the gauge size to regulate his/her frequency of checking.

Here, results with humans showed a high variability of the distance / gauge size relationship between subjects. In particular, for many subjects the relationship appeared to not follow a linear trend. We thus quantified for each subject the departure from linearity by extracting 3 parameters from the mean distance to check/gauge size curve (see **fig. 2**): 1) the slope of the line joining the first and last point of the curve (i.e. smallest and largest gauge sizes); 2) the area under the curve (AUC) between mean distance to next check curve and the modelled line; and 3) the maximum orthogonal distance between the line and the curve.

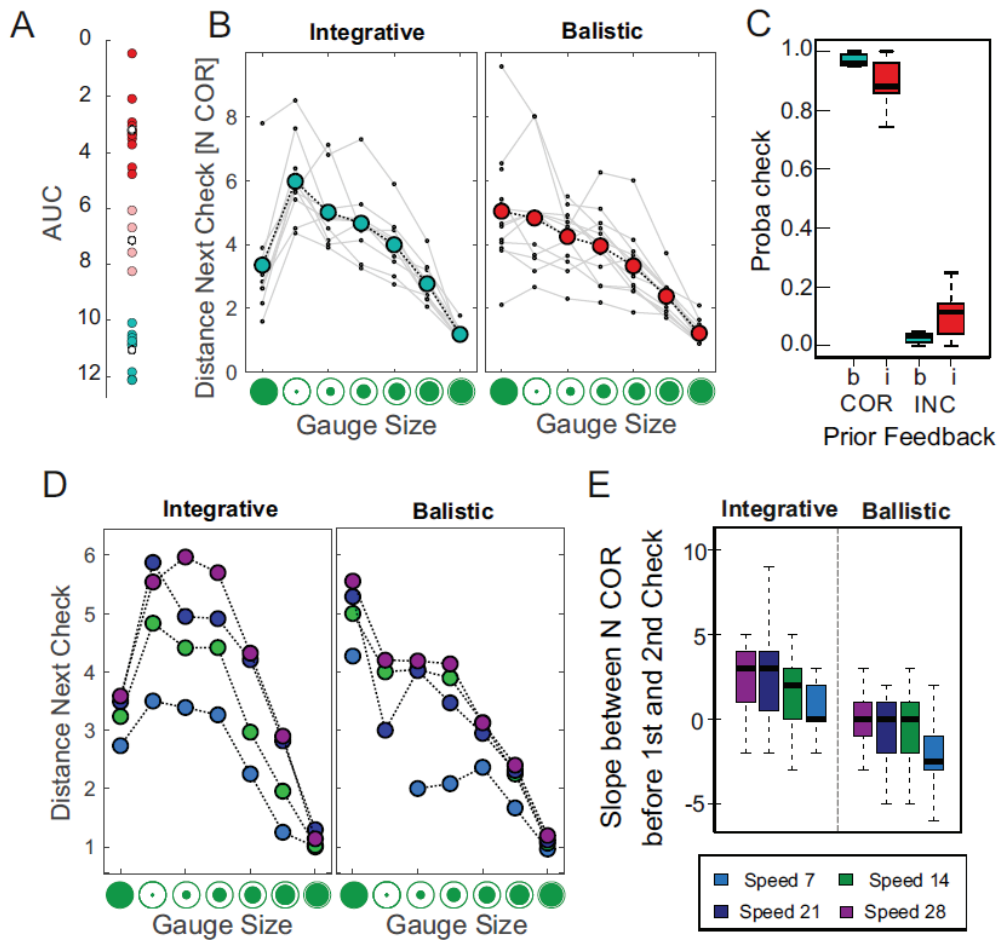


Figure 2. Division of subjects based on the strategy used to regulate decisions to Check. **A.** K-means clustering result for 3 groups based on AUC. The white point is the mean per cluster. **B.** Effect of observed gauge size on checking. The plots show the number of correct answers (distance) before the subject will next check, and how this varies based on the observed gauge size at the previous check. The data are displayed for the 2 main clusters generated, reflecting different strategies: Integrative and Ballistic. **C.** The type of strategy (cyan: Integrative, red: Ballistic) has an effect on the probability to Check after the different feedback in the visual discrimination task. **D.** The effect of different speeds of gauge size increase on the distance to the next check for the Integrative (left) and Ballistic (right) strategies. **E.** The slope between the number of correct answers before the first check and between the first and second checks. This plot illustrates how the Integrative strategy uses the information of the gauge size observed in the first check to estimate the speed of the problem and regulate the second check - if the problem

presents a slower speed the subject will wait more to accumulate more points before re-checking.

Using these parameters, it appeared that subjects could be grouped according to their pattern of checking. We applied K-means clustering based on the 3 parameters above and generated 3 groups of subjects. A reduction of parameter (eliminating first the maximum distance, and then the slope of the line) did not affect the classification, leaving the AUC as the sufficient parameter to cluster subjects into 3 groups (**Fig. 2A**):

Ballistic. (n=13) The participants adopting this strategy accumulated a larger number of correct answers before checking for the first time, and then increased progressively their frequency of checking until the end of the problem (**Fig. 2B left**). One hypothesis is that checking for these subjects were mostly driven by the prospect of obtaining the bonus or avoiding the penalty.

Integrative. (n=10) These participants' strategy was characterized by early checks, potentially used to estimate the gauge speed of change, followed by sparser checks, and a final acceleration of checking when approaching the full gauge (**Fig. 2B middle**). This strategy, appearing in the quadratic shape of the distance/gauge size curve, allowed subjects to spend more time accumulating points before accelerating the checking frequency to capture the full gauge on time. One hypothesis is that, in this group check decisions were driven by two different motivations: initially to gain information about the speed of gauge increase, and then later to capture the bonus reward or avoid the penalty.

Mixed. The third strategy is apparently a midpoint between the two previous strategies, but it will not be considered further due to the small number of subjects involved (**Fig. 2B right**).

We investigated further how the 2 main strategies would impact on subjects' behaviour in the task. Both groups of subjects (Ballistic and Integrative) made checking decisions mostly after positive outcomes in the main task and rarely after negative outcomes, but Ballistic subjects tended to make significantly less difference between the

2 cases (logistic regression on [Check, Play], PreviousFeedback x Strategy interaction: Estimate = -0.85, Standard error = 0.19, z-value = -4.6, p-value = <0.001) (**Fig. 2C**). This might suggest that Ballistic subjects were more tempted to check after any trial to verify the current state of the gauge, whereas the Integrative group was more efficient (or more aware of the task structure), as gauge size increases could occur only after positive outcomes. Moreover, the integrative strategy stood out over the ballistic in that the checking pattern additionally adapted to the speed of gauge size in the problem, which reinforces the idea of a deeper integration of the gauge information into checking decision making (**Fig. 2D**). We evaluated the quadratic shape of the checking pattern and its modulation by the gauge speed using a linear mixed-effects model including orthogonal polynomial fits (where the model tests orthogonal quadratic and linear fits) for the gauge size and the potential interaction with gauge speed. Applied to both groups separately, the model revealed a significant quadratic fit with gauge size interacting with gauge speed only for the Integrative group (Integrative group, quadratic * speed interaction: Estimate = -1.45, Standard error = 0.58, z-value = -42.49, p-value = <0.013; Ballistic group no significant interaction for the linear z-value=-0.1, p=0.92 or quadratic value=-0.24, p=0.81 fits).

In order to evaluate the effect of the information received during the first check, we calculated a slope between the number of correct responses before the first check, and the number between the first and second checks, for each of the 4 available speeds (**Fig. 2E**). This slope should be positive if subjects slow down checking, and negative if they accelerate checking. Participants who showed an integrative strategy had positive slopes on this measure – they checked early (mean +/- standard deviation 1st Check: 3+/-2 COR) and then decreased the frequency of their subsequent checking putatively based on the estimate they make of the speed of the gauge increase (mean standard deviation 2nd Check: 5 +/- 2 COR). Indeed, the slope of the slowest problems (speed = 28 points) was different from the two fastest speeds 14 (linear mixed-effects model, Speed 28 vs 14: Estimate=-1.09, Std. Error = 0.55, df = 163.56, t value = -1.98, p-value = 0.049) and 7 (Speed 28 vs 7: Estimate=-2.03, Std. Error = 0.52, df = 163.83, t value = -3.91, p-value = 0.0001), which implies a discrimination of slow (28 and 21 points), medium (14 points) and fast (7 points) speeds. In contrast, data for the participants applying the ballistic

strategy only showed a difference from zero in the case of the fastest speed (Speed 28 vs 7: Estimate=-1.45, Std. Error = 0.50, df = 207.87, t value = -2.90, p-value = 0.004). These participants were slower to start to check in a block (1st Check after on average 5+/-3 correct trials), thus in case of the fastest speed, the first check would reveal a larger gauge and thus the imminent bonus availability. In this case subjects directly increased the checking frequency.

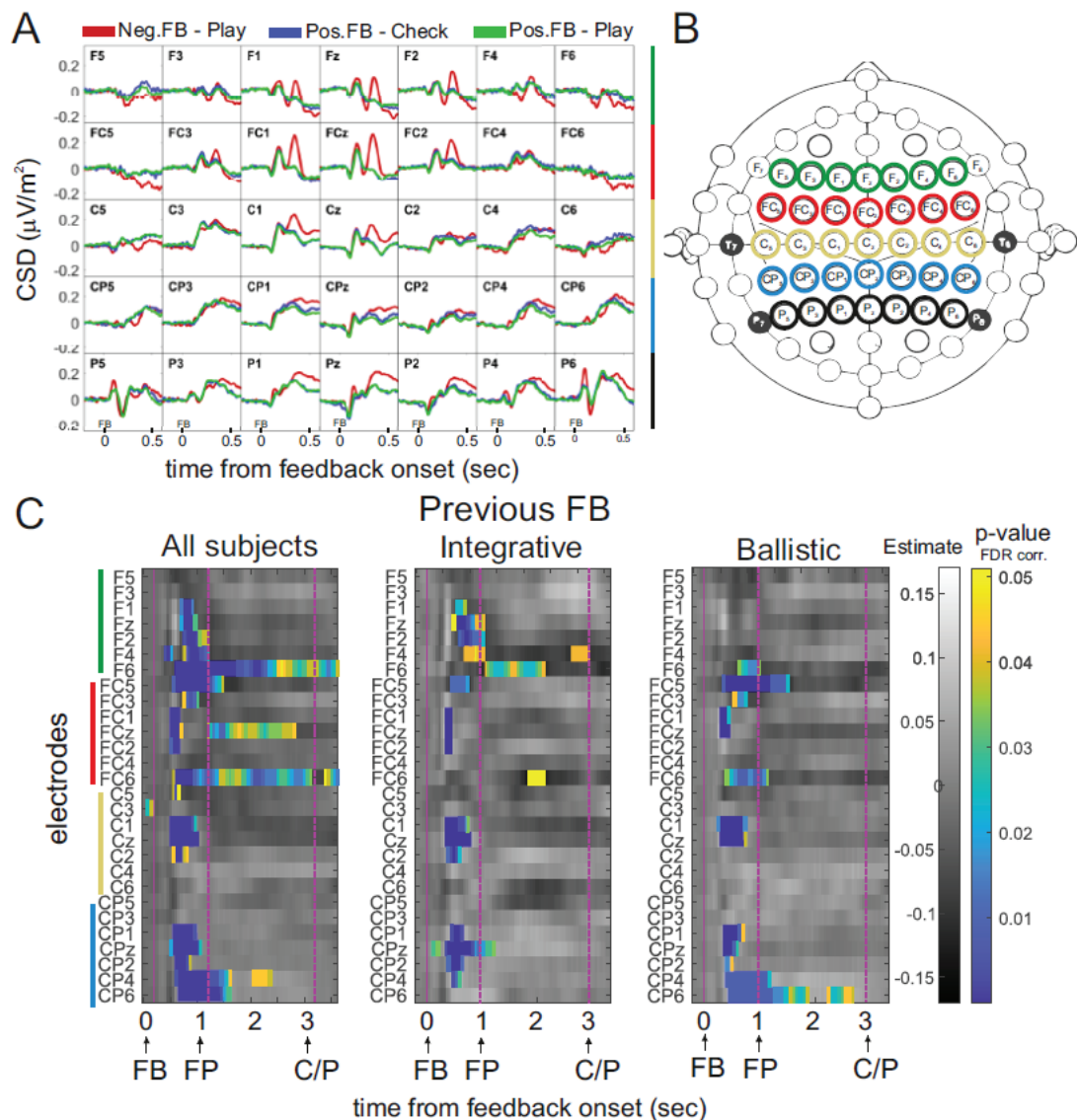


Figure 3. Effect of Feedback valence (COR/INC) on ERP amplitude (CSD). A. Feedback-related potentials obtained at a subset of electrodes (names in inset, row associated to colour corresponding to panel B). The figure shows FRP for negative

feedback that are followed by a decision to play (red), and positive feedback followed by a decision to play (blue) or to check (green). B. The figure displays on the left the 64 electrodes cap arrangement with colour surrounding those displayed on the statistical display (right). C. The statistical maps on the right show the model estimate values (gray scale) and, on top, the significant p-value with FDR correction. Considering all subjects (left), the group that applied the Integrative strategy (centre) and the group that applied the ballistic strategy (right). Figures are centred on the feedback onset (FB). At $t = 1s$, the onset of the fixation point (FP), followed by the intertrial interval leading to the Check or Play options onset (C/P).

Neural dynamics linking performance monitoring and decisions to check

The behavioural investigation revealed that subjects used both information from performance in the Main task and the information gathered from checking the gauge to regulate checking decisions. Such strategy however varied between subject groups. We thus searched for neural markers of those strategies in EEG signals recorded during the task performance. We seek for indices of the strategy used by subject to use or not particular information to regulate decisions.

Markers of performance monitoring have constantly been observed at the time of feedback of performance in feedback-related potentials (FRP) or oscillations (Cavanagh & Frank, 2014; Cohen et al., 2007; Sallet et al., 2013, Viñales et al. submitted). In a first series of analyses we tested whether the FRP and ensuing signal until the decision to check or play (3 seconds) would be modulated by 3 factors relevant to adaptation and decision to check: the feedback valence (COR/INC), the gauge size (potentially stored in mind by subjects), and the future decision to check or play.

The amplitude analysis of the CSD signal did not show significant changes related to gauge size or decision to Check / Play. Significant variations related to feedback valence were observed in the first second during feedback onset (see **fig. 3**), corresponding to the well-known FRP with maximum peak at frontal central electrodes. When all subjects ($n=23$) were analysed together, a sustained feedback valence effect was observed during the intertrial interval especially for FCz, F6, and FC6 channels. We tried to separate data

by strategy groups (Ballistic n=13, Integrative n=10), but the statistical analysis, after FDR correction, retained mostly the effects locked to feedback onset (**Fig. 3**).

Several studies have shown that oscillations in different frequency bands are modulated by attentional load, reinforcement values or other task-related parameters. We tested whether the factors described above, including the linear or quadratic transform of the gauge size would explain some variance in the power spectrum density (PSD) (see methods). PSD analyses were thus performed across all subjects (see **figure 4**), for 3 epochs defined between the feedback onset and the check/play decision time, and using the linear mixed-effects model described in methods. Figure 4 illustrates the outcome across all subjects. First, note that the tested 3 factors modulated the power in some frequency bands and across electrodes differently for the 3 epochs, mostly on theta-alpha and in a wide beta to gamma range (24 to 44 Hz) and in the theta band for the feedback factor. This first suggests that those factors had differential impacts over the successive stages following feedback onset and leading to decisions, and second that those influences play at different frequency ranges.

The valence of the previous feedback (COR/INC) modulated oscillations power mostly over frontal and central electrodes, and at low frequency bands (Theta and Alpha/low beta) potentially corresponding to the FRP wave. During the next 2 epochs the valence effect spreads over parietal electrodes and then fronto-central (FC) ones toward reaching the decision point. The spread also became more predominant in the high beta-gamma range.

Interestingly the quadratic fit for Gauge size revealed significant modulations within the 1sec following feedback onset and for Fz and other fronto-central electrodes (**Fig. 4 top row**). This played mostly on alpha and beta to gamma oscillations. In the following the Gauge size effect was mostly linear for signal on the most frontal tested electrodes and some central electrodes (over sensorimotor areas contralateral to the hand used) in the last epoch when the decision to check or play was prepared.

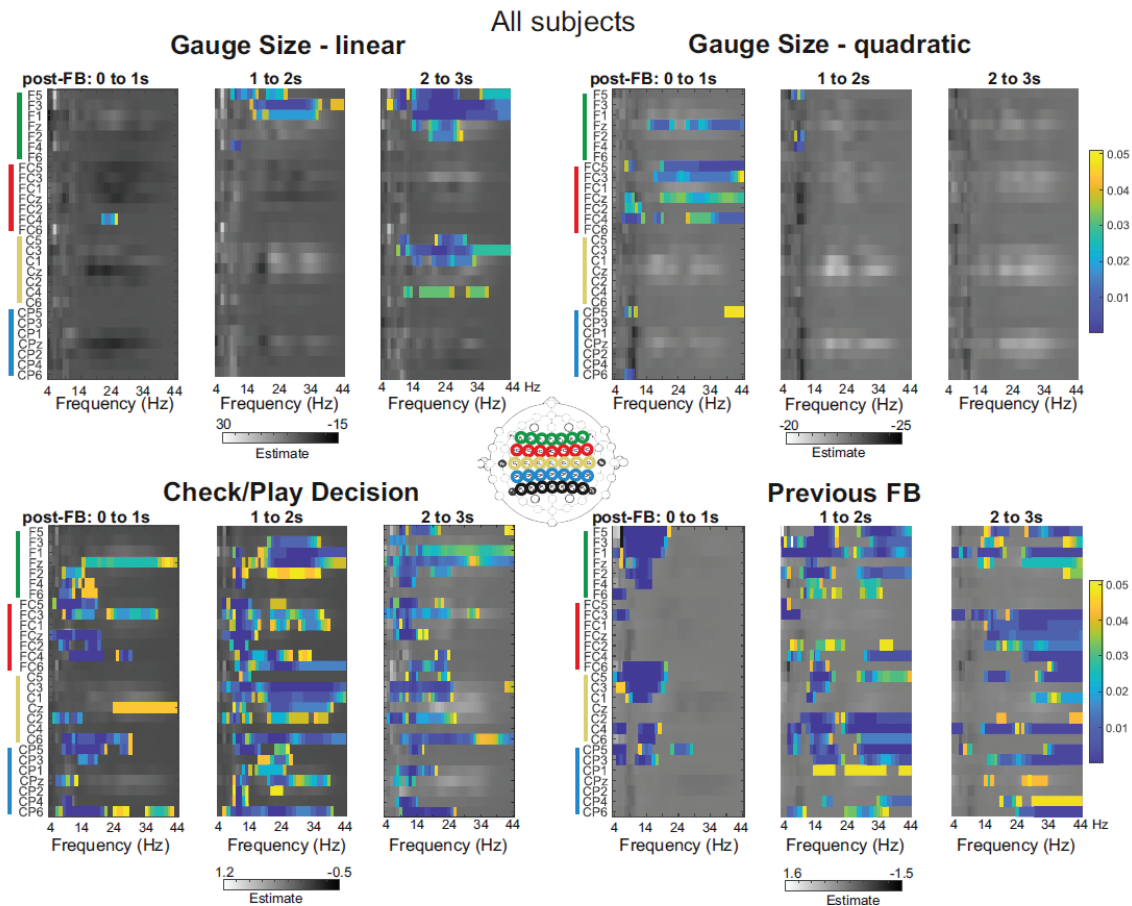


Figure 4. Modulation of power spectral densities across electrodes by 3 factors: Gauge Size, Check-Play decision and feedback valence. The image shows the model estimates value in grey scale and the significant p-value with FDR correction in colour. Data are given for the two orthogonal polynomial fits for Gauge Size (linear and quadratic). The effects of the 3 factors are show for 3 epochs constituting the time between the feedback onset (at 0) and the onset of the options to check or play (at +3 sec).

The Check vs Play factor on the contrary had a widespread influence across all epochs in theta and beta bands. The effect was overall stronger (in size and number of electrodes) in the last epoch but for lower frequencies than in the second epochs. Note however that because the locations of options Check and Play where not alternated from trial to trial, we cannot interpret the Check-Play factor as solely related to a specific checking decision versus play decision marker. It could simply reflect orientation of

attention toward either side of the screen where the options were to appear. Yet the temporal course of encoding this factor would still reflect the timing of internal process related to such decisions.

Checking strategies are reflected in power spectrum and time course.

Subjects demonstrated different checking behaviours which putatively corresponded to 2 different adaptive gathering and use of gauge size information. Subjects were grouped according to these 2 strategies characterized by quadratic versus linear influences of observed gauge size on checking frequency in the so-called integrative and ballistic groups respectively. Because EEG recordings showed, across all subjects, both quadratic and linear representations of the gauge size but at different times in the inter-trial periods, the question remained of whether these effects would reflect the different strategies used independently by the subgroups of subjects. We thus carried out the preceding analysis separately for the 2 groups: integrative and ballistic. The analysis led to 3 major results (**Fig. 5**).

First, data from the integrative group presented a quadratic effect, in accordance with their strategy, in the theta and beta gamma ranges, and for Fz, frontal and fronto-central subsets of electrodes. It occurred mainly for the 1st time window (during feedback on), although some effect could be detected in the later epochs in the beta range. Some linear effects were found in the second epochs in FC electrodes.

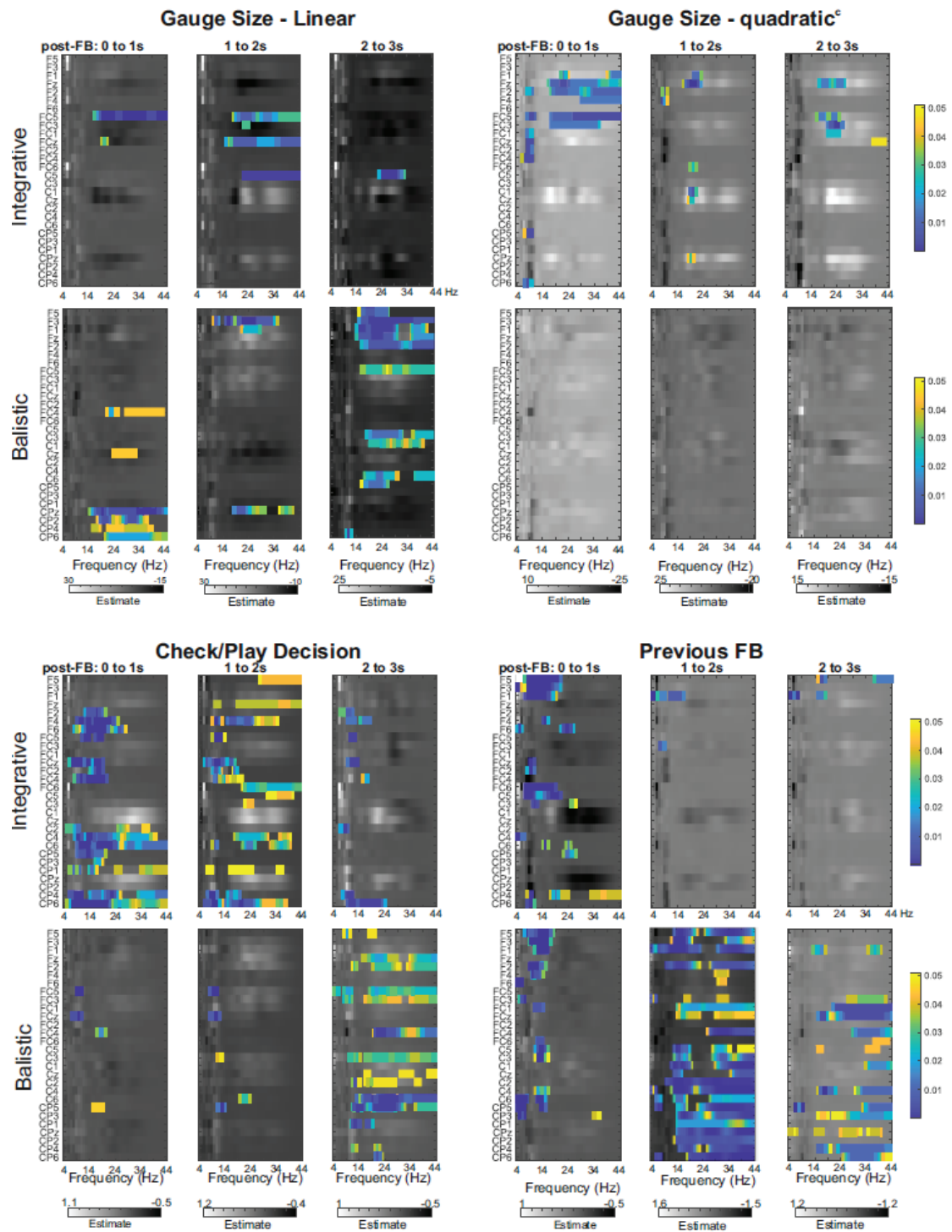


Figure 5. Factors in linear mixed-effects model at PSD per Strategy Group. The image shows the model estimate value in grey scale and the significant p -value with FDR correction in colour in factors: Gauge Size, Check or Play decision and feedback valence. Data are shown separately for each strategy group (Integrative and Ballistic) for PSD between 4 to 45Hz, in 3 time-windows between feedback onset and onset of check/play options.

Second, recordings in the ballistic group showed no significant quadratic fit, but linear ones in CP electrodes at the time of feedback and in central and frontal electrodes before the decisions to check or Play. This again is in accordance with the strategy used by these subjects to regulate checking decisions.

Third, the contributions of the check vs play decision and feedback valence to power spectrum modulations had almost opposite time courses in the ballistic and integrative groups. Indeed, while the integrative group revealed theta and beta gamma modulations for check/play and feedback early in the intertrial (first epoch), the ballistic group showed more massive modulations in the second and third epoch for feedback and just before decision for the check/play factor.

In conclusion, oscillatory power, especially in the beta to gamma range, reflected subject strategies in 2 ways: first by representing a transform of the gauge size in adequation of its strategical use, and second by the time course of the influences of feedback and decision to check or play.

Fronto-frontal synchrony and decision making.

Monkey recordings have shown that during an equivalent check/play protocol neural activity in medial (midcingulate cortex) and lateral prefrontal cortex display differential activity and coordination during decisions to check and play compared to externally triggered decision in the main task (Stoll, Fontanier, et al., 2016). This suggested that the two regions are coordinated during decision making but that the strength or direction of coordination was context dependant. We thus seek whether we could at least show particular time relationship and functional connectivity in human EEG during decisions in the task. This was also motivated by previous studies showing medial to lateral frontal synchrony in human EEG related to performance monitoring and adjustment in cognitive control (Cavanagh & Frank, 2014).

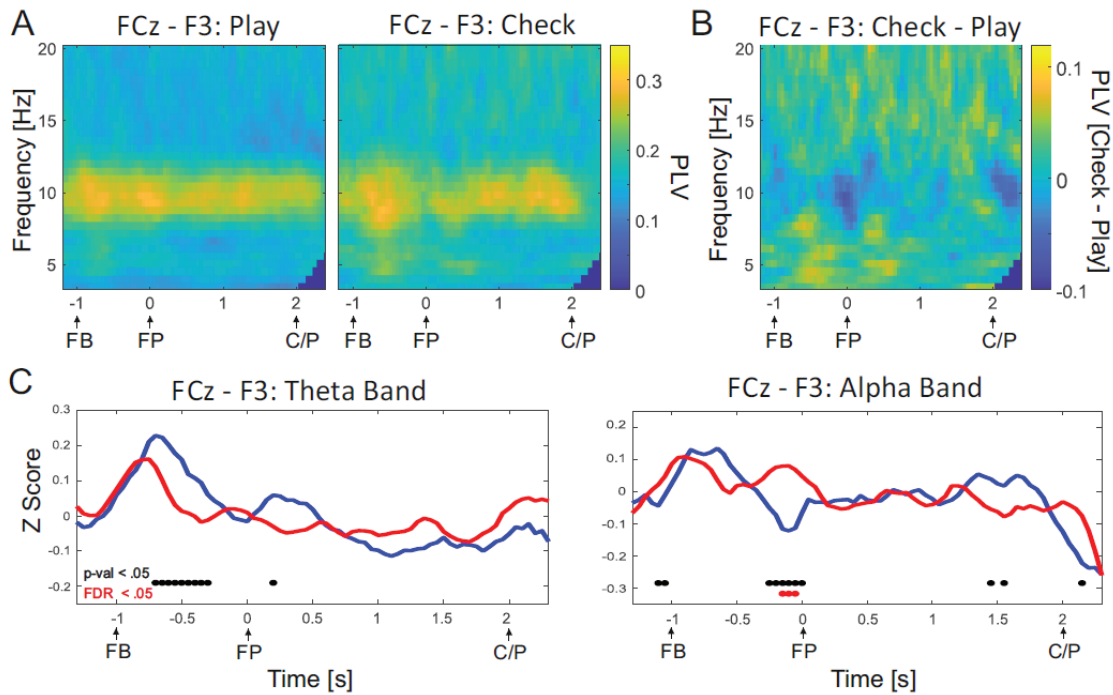


Figure 6. Phase synchronization analysis for decision Check / Play between FCz-F3 channels. (A,) PLV value in time from 300ms before the feedback (FB) and up to 300ms after the image to execute the Check / Play decision (C/P), at frequency band from 4 to 20Hz, between the FCz and F3 channels, for the Play and Check choices. (B) presents the PLV difference Check - Play. (C) Z score of the PLV value, normalized considering the entire time window analysed for theta band [4 - 8Hz] and alpha [8-12Hz], **Check (blue) and Play (red)** in both cases, previous positive feedback. In black the time moments in which the p value without correction is significant in difference between Check and Play (value less than 0.05) are represented, in red point where FDR present significant in difference between Check and Play (value less than 0.05).

We computed phase locking (PLV) between FCz and F3 (contralateral to the used hand) for Play and Check choices after positive feedback. **Figure 6** shows that for both cases synchrony in the alpha band was sustained during the intertrial period until the time of options onset (and onset of the response) where it shows a desynchronization. The time-frequency diagrams also reveal increased phase locking in the theta band for check trials in particular. The difference in PLV between check and play (Check-Play) (**Fig. 6B**), shows that alpha was reduced in check compared to play at the offset of FB and just before the

play choice. However, a larger synchrony in theta appeared during and after feedback for check trials compared to Play in multiple successive bins. Focussing on theta and alpha band for statistical purposes we tested the difference in FCz-F3 synchrony across subjects. **Figure 6C** shows the Z-Scored PLV values and the statistical outcomes. The increase theta and reduced alpha in check compared to play at the time of feedback was significant but not after FDR correction for the theta increase (Wilcoxon test across subjects at each time bin on z-scored PLV). Decreased alpha synchrony .5 seconds before the check/play option and reversal at the onset of the options were significant but not after FDR correction.

When separating subjects by strategy groups, none of the effects survived FDR correction. However, uncorrected p-values revealed consistent tendencies for both groups: increased theta synchrony during feedback and decreased alpha synchrony just before feedback offset in check trials compared to play. In addition, the decrease in alpha for play compare to check before check/play options was also observed in both group at $p < .05$ uncorrected (supplementary figure). Note again that the small sample sizes of subgroups (Ballistic $n=13$, Integrative $n=10$) made it difficult to pass FDR correction.

We studied further the PLV values looking at the decision and response in the main task, where subjects decided to choose Left or Right targets (**fig. 7A**). One can note alpha synchrony during the delay between cue and response, with a desynchronization at response onset. The Left-Right contrast (**figure 7B**) revealed no apparent difference in theta or alpha bands. No left-right difference was found in at least 2 successive bins, even at uncorrected thresholds in theta and beta bands (**fig. 7 right**).

DISCUSSION

In this study we observed that human subjects could develop different strategy to regulate checking decisions in our protocol, and that frontal power spectra (acquired with EEG) revealed markers of performance monitoring and strategy application.

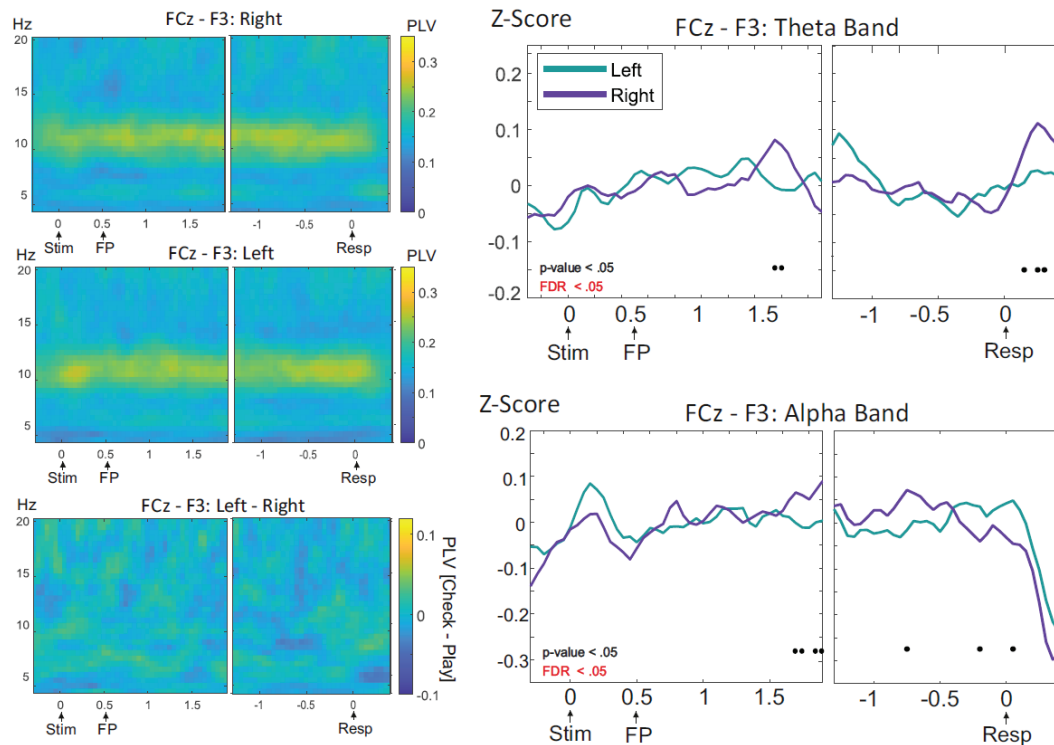


Figure 7. Phase synchrony analysis for Left / Right decision in mean task between FCz-F3 channels. (A) PLV value in time from 300ms before the appearance of the stim (bar with inclination) and up to 1.4s after the fixation point ($t = 1.9s$) and from 1.3s before the decision image Let / Right y up to 300ms after this, in frequency from 4 to 20Hz between FCz and F3 channels, for the left and right choices. (B) Presents the Left-Right PLV difference. (C) Z score of the PLV value, normalized considering the entire time window analyzed for theta band [4 - 8Hz] and alpha [8-12Hz], Left (light blue) and right (purple), in black the temporary moments in which the p-value without is significant in difference between choosing option on the right / left (value less than 0.05).

The design of the protocol induced subjects to use multiple information to regulate checking frequency. Because the gauge size increase, and thus the possibility to get the bonus (avoid the penalty), was related to gains of points in the main task, decision making in this task has to balance performance in the main task and regular checking to optimize bonus gathering. Human subjects in the current study and monkeys in previous work (Stoll, et al., 2016), regulated these decisions mostly in similar ways, by choosing the play

option in about 80% of trials (average 81.3% in humans on average, 87.5% in the monkey study). Regulation of checking frequency was taking advantage of the main features of the task: increased checking likelihood after a positive feedback in the main task, and increased frequency with increased gauge size, in humans as well as in monkeys. Subjects also used the gauge size observed upon checking to regulate the checking frequency. However, we show here that humans displayed 2 types of checking strategy, one (integrative) which efficiently used the task features to optimize checking, and one (Ballistic) which might have been more driven by the prospective to get the full gauge. In any case behavioural analyses revealed that subjects integrated multiple information to build and regulate, across trials, the decisions to check.

The EEG analyses performed on 3 epochs during the interval between feedback from the Main task and the onset of the Check-Play option, showed that check vs play differences could be observed throughout the inter-trial interval when all subjects were considered. However, breaking down by strategy groups revealed in fact that the contribution of the Check/Play factor to the variance in power appeared with different time courses depending on subjects' group. More precisely, variations in higher frequency bands indicating the incoming decision appeared early in the intertrial for the integrative group, but at the very last second for the ballistic group. Taken together with behavioural data indicating that the integrative group was more careful about linking feedback to check decision, this supports the idea that those signals reflected the dynamic of the voluntary decision process in the intertrial period. A recent study of sEEG recordings in humans revealed indeed how voluntary decisions can be decoded from high gamma activity recorded in frontal areas (Thiery et al 2020 Plos Biology). Data from the integrative group (Fig. 5) showed that the Feedback-related variations present in both group at low frequency (as observed in numerous previous studies, e.g. see Cavanagh & Frank, 2014; Cohen et al., 2007) was accompanied at the time of feedback (0 to 1 sec after feedback onset) by fronto-parietal beta oscillation and beta gamma modulation by the decision to check or not. This was absent in the ballistic group. Multiple studies have addressed the mechanistic role of midfrontal feedback-related activation in the regulation of cognitive control (Cavanagh & Frank, 2014; Clay B. Holroyd & Coles, 2002a; Shenhav et al., 2013). Recordings in epileptic patients have shown that negative feedback related cingulate

activation follow the earlier feedback-related activation in the anterior insula (Bastin et al. 2016 Cerebral Cortex). Such data suggest that mid-frontal (cingulate) feedback -related activity reflects a process downstream to pure feedback detection, potentially more related to integrative functions. The current correlational data (in opposition to causal and interventional data) including the variations of time courses of modulations between subject groups would fit with the idea that feedback-related information is integrated by mechanisms supported by or reflected in beta to gamma frequency oscillations, and that contribute to the decision process. As in monkey single unit recordings, the temporal course of neural decoding for the different variables relevant to decisions to check showed the progression of decisions steps (Stoll et al., 2016).

Information about observed gauge size and the putative mental 'simulation' of its progression across trials by the different subjects were reflected in the frontal beta-gamma range in both groups of subjects with modulations coherent with the strategy observed for each group. Beta oscillations have been associated to various mechanisms related to cortical processing, maintenance and attentional control in frontal areas (Engel & Fries, 2010; Stoll, Wilson, et al., 2016b). One interpretation is that modulations in those frequencies, with varying time course according to strategy, reflected the recruitment of active processes rehearsing and manipulating the gauge representation in order to inform the decision to check or not. Such rehearsing or re-instantiation of representation of the gauge has been observed in monkey MidCingulate cortex before decisions to check/play in a similar protocol (Stoll et al., 2016).

Medial-Lateral synchrony and decision making.

Decisions made within a cognitive state, i.e. by means of the currently used task set or cognitive mapping, are theoretically different from decisions leading to state shifting (Kolling and O'Reilly, Domenech and Koechlin). The later concern exploratory decisions, in foraging context or in situations where behaviour departs from default actions. Such decisions are supposedly triggered by monitoring signals evaluating the value to switch from current actions. Performance feedback, changes in outcome trends, or prospective planning contribute to such switches and involved medial and lateral frontal areas (Kolling et al., 2016, 2018; Procyk et al., 2000; Quilodran et al., 2008b). In the original

monkey version of the Check-Play task, changes in MCC neural dynamics during internally-informed Check decisions (as well as during feedback processing) preceded LPFC changes, while the reverse was observed for decisions guided by memorised visuospatial information during the Main task (Stoll et al., 2016). Neural activity in MCC was also more dynamic during check decisions than during decisions to play.

In the present study we searched whether such difference in neural dynamics between decision type could be observed with EEG in humans. We observed a stable tendency for differential synchrony between medial sites and lateral sites (in theta and beta bands) in cases of decision to check at the time of feedback and just before the check choice. However, most effects (apart from those in alpha band at feedback) did not survive FDR correction. We compared to decisions to choose the left or right target (i.e. with a spatial mapping similar to the Check vs Play decision) in the main task and found no sustained or coherent differential synchrony in theta or alpha bands.

Overall, the EEG data showed some reflection of differential neural dynamics between state-shift decision and within-state decisions. Further analyses are required to describe the dynamics of check decisions at more large scales within the electrodes space.

Limitations of the study

One main interesting element of the current study, the identification of subgroups of subject with different checking strategy, is also one of the major limitations. Indeed, the initial sample size of $n=27$ subjects was subdivided in half approximately leading to really low subject sample sizes for the analyses. This might have been particularly detrimental to the analysis of PLV in the 2 subgroups.

The time course of processes during the intertrial still needs to be studied at large network scales considering the multiple frequency bands at which signals were observed. Cross-frequency couplings of different types can contribute to different brain functions (Hyafil et al., 2015). This will need further investigations, in particular to apprehend the

fronto-parietal dynamics shown to contribute to feedback processing and decisions to check.

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5. Discussion and Perspectives

5.1. Neural mechanisms of adaptive behavior based on relevance of information

The first study developed in this thesis evaluated, by means of electroencephalography, the modulation of the FRN potential and oscillations as a function of the relevance of the information for the adaptation of behavior, during the execution of a trial and error test in humans. The potential FRN showed a selective character between informative feedbacks, regardless of whether its value was negative or positive (incorrect choices in the search process and correct first choice) and not informative (repetition of correct choice). The FRN was reduced in amplitude in response to positive feedback in repetition in accordance with previous studies (Cohen et al., 2007; Sallet et al., 2013).

Beta activity proved to be a particular differentiating factor, presenting an increase in power specifically in response to the first correct feedback, when evaluating frontal channels. This selectivity to correct informative feedback was also reported in a study that used a modified version of the Wisconsin test, which corresponds to a task designed to evaluate executive functions and that also includes an exploration and exploitation phase to deduce classification rules from a set of letters (Cunillera et al., 2012b). While activity in theta, shows an increase in power in response to feedback, similarly to the FRN, although the significance is present only in the comparison between first correct vs correct in repetition.

The study of FRN and its frequency components can provide relevant information on the nature of neural mechanisms that allow the adaptation of behavior based on error processing and decision-making. In this context, the protocol used represents a good evaluation method in the exchange of exploration and exploitation behaviors based on the different types of information received. Due to limitations in the acquisition equipment, a NuAmp EEG with 31 Ag / AgCl unit electrodes, no spatial filters were applied to increase its spatial precision, the application of CSD is recommended for recordings with an electrode density greater than 64.

5.2. FRN and EEG Oscillations: Biomarkers of Cognitive Impairment

With the growing aging of the population, the increase in neurodegenerative diseases is becoming more relevant every day, and with this it becomes an increasingly important challenge for science. Among the most popular pathologies is Parkinson's disease, which affects 1% of the population over 60 years of age (Tysnes & Storstein, 2017).

Epidemiological, clinical, genetic and pathological studies show that the dysfunction of dopaminergic neurons, which gives rise to PD, begins before the appearance of motor manifestations and, therefore, before its clinical diagnosis can be established (Berg, 2008; Gaig & Tolosa, 2009; Stern et al., 2012; Stern & Siderowf, 2010). One of the greatest challenges in PD is to identify biomarkers of the pre-motor stage and evaluate their potential usefulness for early detection PD before motor symptoms appear, a stage where the percentage of dead dopaminergic neurons is the majority (Olanow & Obeso, 2012b).

From this point of view, cognitive biomarkers become relevant since PD patients show cognitive dysfunctions from early stages (Koerts et al., 2009; Muslimovic et al., 2005b) mainly affecting executive functions, including cognitive control mechanisms (Leh et al., 2010; Monchi et al., 2007). Results on measures of complexity and connectivity suggest that specific alterations or interruptions of brain communication can be measured before PD patients develop dementia (Bertrand et al., 2016).

In my thesis, the neuropsychological status has been evaluated, through validated clinical tests for PD, behavioral performance and EEG markers of the performance monitoring functions through a trial and error task in early PD patients, in comparison to healthy controls. The results show some biomarkers alterations used in the study, specifically the increase in frontal beta power which in controls was evoked exclusively at the first positive feedback, in PD patients is not present. Regarding FRN the significant difference that appeared between response to incorrect and correct feedback on repetition is lost, which could explain the tendency to repeat errors that characterize PD patients, and also to pathological gambling problems that they may present (Weintraub et al., 2015).

Although there are not many studies carried out in PD patients evaluating cognitive ERP, a decrease in potentials has been recorded compared to controls (Brown et al., 2020a; Willemsen et al., 2009a). But there are certain factors that can affect the comparison with

our study, the main one: the score on the BDI depression test. Willemsen et al. (2009) worked with patients with an average BDI = 8.2 ± 4.7 and controls with 2.6 ± 2.4 ; the study by Brown et al. (2020) presented PD patients with a score of 7.64 ± 5.23 and controls with a score of 4.93 ± 4.64 , all with a low score of 13, which on the test scale implies that they did not present signs of depression. In contrast, our study presented patients with a score of 13.8 ± 9.1 and controls 10.5 ± 6.1 . The controls in our study have a higher mean score than the studies mentioned, but none reaches 13 points, while in the case of patients, 8 have a score indicating mild or moderate depression. It should be noted that apathy is another factor that has shown an effect on the amplitude of potentials (Martínez-Horta et al., 2014). Therefore, these results call for new studies with higher number of participants in order to generate subgroups of analyzes based on evaluations such as depression and apathy that are associated with PD.

Another study line that opens up with this result is that most of the investigations that have studied the ERP component and the oscillations linked to the presence of feedback (whether positive or negative) in tests that evaluate the cognitive control system and the ability to adapt, have been performed in young subjects between 18 and 30 years old, usually university students and without cognitive impairment. Understanding the changes at cognitive level that occur due to natural human aging is essential to generate programs to improve the quality of life for this population and to understand neurodegenerative diseases.

And the question arises as to whether there is any effect associated with aging in the modulation of information relevant to the adaptation of behavior in cognitive control. An effect of age on the P300 component has been demonstrated in Go/noGo type tests (Kober et al., 2016; Kropotov et al., 2016) and a decrease in theta and alpha bands of EEG oscillations (Dias et al., 2015). With the intention of testing the plausibility of a new project that studied the effect of age on the FRN and oscillations evoked by feedback, test recordings were carried out in 7 young subjects (22.4 ± 2.3 years), to compare with the results of the control population in the Parkinson's study. The recordings were performed with the same set-up and the same Problem Solving Task protocol, in the laboratory of the School of Medicine of the University of Valparaiso Chile, during 2019. The preliminary results are presented in figure 5.1. The average signal for young subjects is compared to the average ERP reported in the controls of the PD group, despite the low recording

number of young group, the image suggests a difference in the ERP amplitude that it would be interesting to analyze in full.

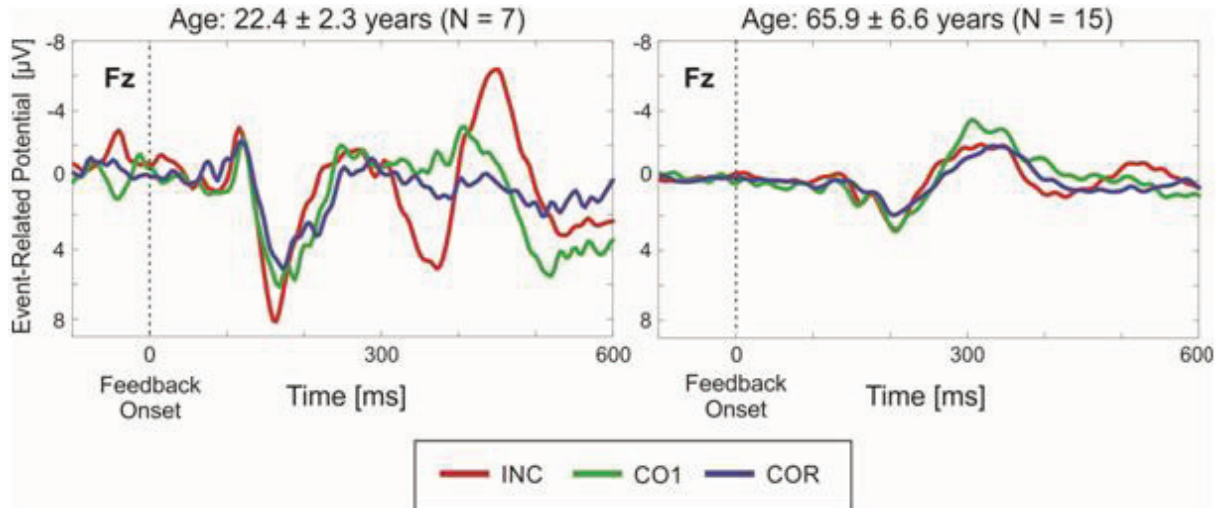


Figure 5.1. Grand-average electrophysiological feedback responses for INC, CO1 and COR trials in in two age groups at electrode Fz. ERP are shown for incorrect response (INC, in red), first correct response (CO1, in green), correct response in repetition (COR, in blue), and are aligned on feedback onset.

5.3. Implementation of Check Protocol

Our need to reduce uncertainty and the probability of error in our actions, prompts us to search for additional information through processes such as verification. Despite the relevant role of these functions in our adaptation process, the mechanisms that drive the decision to verify are not fully defined and their understanding is still a challenge.

The second study presented in my thesis, adapted the experimental protocol designed by Stoll et al. (2016), comparing, as far as possible, their results in monkeys with our results obtained in humans through EEG recordings. This study is part of a larger project, which, at the beginning of my thesis, began with a significant delay due to administrative problems with the ethics committee, which gave the corresponding permits to start in January 2019. The study consisted of 3 stages that posed different challenges for the adaptation of the protocol:

• **EEG Protocol:** 41 subjects performed a session of 4 blocks of 15 minutes, carried out at the SBRI (U1208). The task was implemented in Matlab and Psychtoolbox on Windows 10 platform. Each block consisted of 15 minutes for the participating subject to execute all the possible problems in order to obtain the maximum possible score, inserting the bonus version (where the subject earned a score extra score to be verified at the correct moment) and the penalty (where if it is not verified at the correct moment, that extra score is subtracted from the score). To increase subjects' motivation the score of each participant was stored and displayed at the end of each problem together with the top 5 of the historical ranking among the other participants.

The version with which the study reported in this thesis was carried out (section 4.2) had a fixed position for the options Check (on the left) and Play (on the right), When analyzing the CSD signal centered at the time of executing the response (see figure 5.2 A). When looking for EEG differences between check and play choices, channels such as F5, FC5 and F6 were found to show clear differences, but that could not be related to cognitive states, since the same difference was seen between the left and right responses in the main task (see figure 5.2 B). In reaction to this, a new version was implemented that randomly interspersed the location of Play and Check options on the screen. However, the study could only be carried out in 6 volunteer subjects, preventing representative statistical studies. By averaging the choices Check and Play without differentiating if right or left was pressed (see 5.3 C), it can be seen that the differences in the channels in question disappear. These results modified the implementation of the test that was to be carried out in a future implementation in a MRI study with randomly selected Check and Play locations.

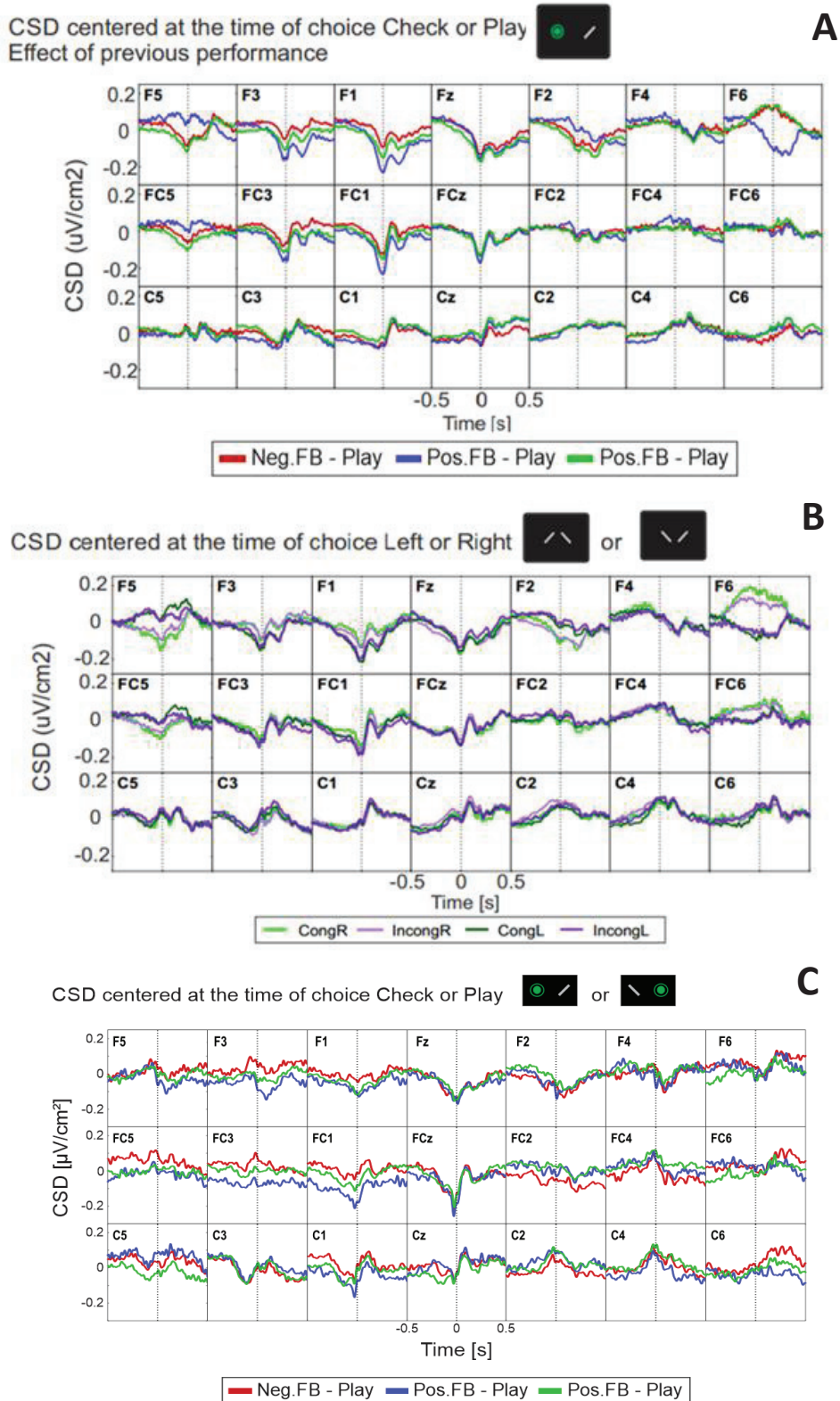


Figure 5.2: CSD centered at response. (A) CSD centered at time of choice Check (pressed left arrow) or Play (pressed right arrow) for selection Check posterior at

positive feedback (blue) and Play after negative feedback (red) and positive feedback (green). (B) CSD centered at time of choice of tilt of the cue to the right or left, this choice has two modes: congruent, when the choice of the left or right arrow coincides with the position of the tilt options (dark green: congruent mode choice of left arrow, light green congruent mode choice right arrow) and inconsistent when these options intersect (dark purple: incongruous mode choice left arrow, light purple mode incongruous choice right arrow). (C) CSD centered at time of choice Check or Play in version with random configuration of the location of the options, for selection Check posterior at positive feedback (blue) and Play after negative feedback (red) and positive feedback (green).

• **Behavioral Study:** 14 subjects simultaneously carried out 1 session of 4 blocks of 15 minutes at the GATE-LAB facilities (UMR 5824). The lab's simultaneous online registration system involved implementing the task on Octave and Linux. The times and parameters of the first version of the EEG protocol were maintained, but the display system of the top 5 ranking was modified to a registration system with online updating that showed the score that the participant accumulated during the task after completing each problem, compared to the top 5 of their peers at the time.

One of the biases that is usually incurred in behavioral testing studies corresponds to the choice of participants. In my EEG study, most of the participants were recruited from the SBRI laboratory or related to the doctoral school of neurosciences, so a predisposition to the long duration of the behavioral tasks and the concentration that they require can be presumed. In the case of the GATE-LAB experiment, the participants came from a business school, not used to this kind of task.

Of the 14 subjects I evaluated under this protocol, 12 presented an understanding of the task that implied overcoming 70% of the problems with successful verifications. This concerned 85.7% of the participants. In the EEG protocol, 90.2% of the subjects exceeded the inclusion cut-off in the study. Taking into account the important difference in the number of participants, it can be seen that the GATE-LAB participants, who could be considered totally naive, demonstrated understanding of the test, in 82% of the cases the subjects decided to verify after obtaining positive feedback (which is the one that gives a

point to increase the size of the gauge), the SBRI group performed it in 93% of the cases after a correct answer (see figure 5.3 B). When visualizing the probability of verifying as a function of the gauge size per block, both groups showed an increase in probability as a function of the gauge size and a percentage of verification when the gauge is complete which was lower in the first block, compared to the rest of the session, suggesting a learning process in understanding the task (see figure 5.3 A). A possible difference might have occurred in the final two blocks of the task. In the case of subjects recorded at SBRI, the percentage of verification when the gauge was complete tended to increase in the last block, while for the participants at GATE-LAB, the 4th and last blocks decreased compared to the 3rd, potentially reflecting the fatigue that some participants verbalized after finishing the task.

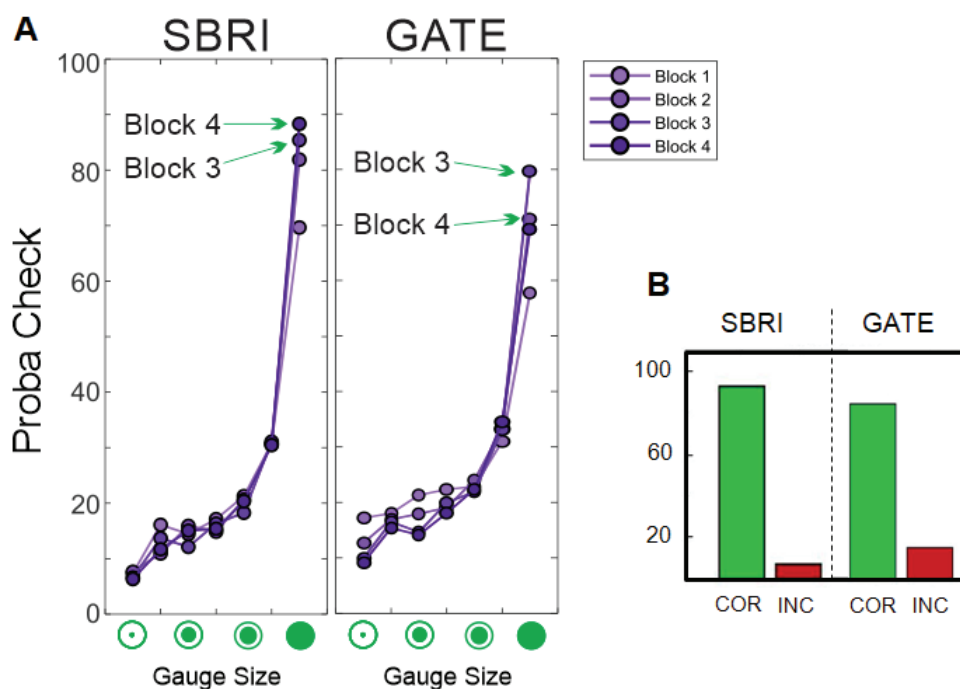


Figure 5.3. Performance comparison in the experimental task of the check decision on different protocols (A) Probability of Check depending on the size of the gauge observed per block of the task and (B) probability of choosing Check based on the performance in the main task, for the participants of the EEG protocol (SBRI: 35 subjects) and the protocol of behavioral study (GATE: 12 subjects).

Given the project of using this protocol in patients with obsessive compulsive disorder, it is a requirement to validate the performance of individuals without pathology or disorder that affects the cognitive level, so that this protocol becomes more relevant

- **MRI Protocol:** 19 subjects executed 2 sessions of 6 blocks of 15 minutes carried out at the imaging center CERMEP. Due to laboratory conditions, a first test was implemented in Octave and Psychtoolbox on Linux, until the definitive conditions were enabled that allowed the use of the same combination as for the EEG protocol: Matlab and Psychtoolbox on Windows 10. This task was implemented based on the results obtained from the other protocols, the random exchange of the position of the Check / Play options, and given the non-differentiation reported between the Bonus and Penalty versions, it was decided to implement a different methodology: having 6 blocks of a first session starting with the Bonus option, 3 Bonus blocks were executed followed by 3 Penalty blocks, while the order was reversed in the second session. This design was made hoping that the continuity between block types would allow an adaptation and a variation when changing.

In addition, since the task must be synchronized by means of TTL with the scanner, the eye tracker system (EyeLink) and a BIOPAC MP160 acquisition system for recording Plethysmography and Breathing I work with the team to resolve this technical aspects. The MRI protocol also included a session for Motor Mapping (localizer tasks) and Resting State.

5.4. Search and use of information to generate strategies

From the behavioral analysis in the test, it was observed that monkeys and humans demonstrated a modulation of the decision to verify based on 1) the result obtained from the main test, where only positive feedback determines progress and produces the increase in gauge, and 2) The size of the gauge, the verification is carried out more frequently as the progress of the test approaches the end of the problem, and therefore, the gauge has a larger size.

The great difference in the modulating strategy of the verification was observed at the beginning of each problem. The behavior in this stage allowed to differentiate two strategies that regulated the control decisions. A group of subjects opted for an early

verification and apparently, used the information on the observed gauge size to estimate the rate of increase of the gauge in the problem to be solved. This strategy was called Integrative. And the second strategy seems to focus on the potential of reaching the full gauge, accumulating a greater amount of positive feedback at the beginning of the problem, and then increasing the frequency of verification as the end of the problem approaches, this strategy was determined Ballistics .

The possible categorization of control strategies is one of the main results presented by this study, but at the same time it implied one of its main limitations when dividing the initial sample of participating subjects. Furthermore, a third group was not considered due to its low presence (4 subjects), which represented an intermediate strategy between Integrative and Ballistics. This leaves a pending study with a larger number of participants that allows the creation of representative subgroups based on the strategy used in this test. Determining the monitoring of uncertainty, as a fundamental aspect of normal cognition, constitutes a key challenge to understand abnormal decisions in psychiatric diseases (Uddin 2021), such as patients with obsessive compulsive disorder who have demonstrated a hyper-reactive monitoring and learning system (Ullsperger et al. 2014) and, in certain studies, have shown an increase in the frequency of verification (Hauser 2017, Voon 2016) affecting the quality of life of those who suffer from a quality of life condition (Cavedini, 2006).

By integrating the behavioral data from the EEG and behavioral (GATE) protocols, the division by strategy that I observed is strengthened, with the intermediate option between Integrative and Ballistic becoming more representative (see Fig. 5.4). The strategies suggest a difference in how the task is approached depending on how the information gathered by checking the gauge is handled. The biggest difference would be in the decisions made at the beginning of each problem, triggered by the information received at the first check. The Integrative group apparently made an estimate of the speed of progress of the task. If these subjects estimated that the rate of increase of the gauge size was slow, hence that many more points were required to finish the problem, they increased the delayed the next check until the size of the gauge indicated that the end of the problem was near. On the contrary the Ballistic group, increased the frequency of verification after the first check simply following the progression of the task, with a near linear relationship to the gauge size change. For its part, the Mix group represents a midpoint between the

other strategies, demonstrating a more conservative behavior regarding the estimate made after the first check, compared to the Integrative group.

In general, the analysis of strategies that determine when to check the gauge identified two stages: the beginning of the block, where small gauge sizes were displayed, and the final phase, where larger sizes were displayed. These two stages could be differentiated by the motivation with which checking were carried out. The final stage presents a common pattern among the 3 proposed strategies, which implies a progressive increase in the checking frequency that is correlated with the increase in gauge size, the objective is to carry out the verification at the moment of full gauge, in order to get the bonus or evade the penalty. The initial stage, however, that differentiated Integrative and Mix from Ballistic groups would be characterized, for the former, by checking motivated by a need for information to estimate the speed of the problem. This information seeking stage might contribute to the strategical regulation of checking based on the structure of the task and not on the single objective to get the bonus (avoid penalty).

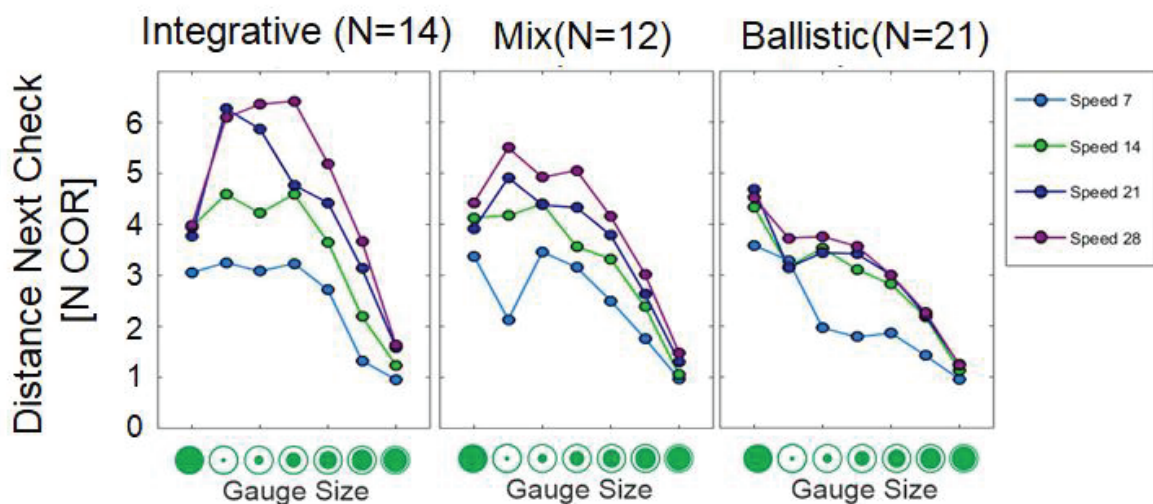


Figure 5.4. Strategy analysis combining EEG and behavioral protocol. The effect of different speeds of gauge size increase on the distance to the next check for the Integrative (left), Mix (center) and Ballistic (right) strategies.

5.5. Dynamics in frontal regions that contribute to decisions to check

The results of the EEG analysis reflected certain neuronal dynamics before the decision to verify, being analyzed from the factors: gauge size, the decision to verify or execute the main test and the feedback prior to such decision, during different time windows. In response to feedback, it is possible to visualize significance at low frequencies, but as the decision moment approaches (inter trial time) the significance appears at beta gamma frequencies. In particular, this activity at a higher frequency is modulated by the verification control strategy used.

The activities in fronto-central electrodes and the indicators of synchrony obtained between the FCz and F3 channels are in accordance with the theories that establish that the MCC - LPFC interactions contribute to the monitoring and evaluation of relevant behavioral feedback and trigger specific adaptation strategies. including exploratory choices, and the construction of prospective values to guide sequential behaviors (Cavanagh & Frank, 2014; Khamassi et al., 2015; Kolling et al., 2018) and with the results that indicate that MCC neurons encode search decisions self-initiated information systems (Stoll, et al., 2016).

In the EEG analysis, and especially in the phase synchrony study, the limitations implied by dividing the participating subjects into subgroups to analyze the various dynamics that underlie the implementation of a different strategy to determine the effects become even more evident. moments of verification.

The EEG recording was the first stage of the subjects participation to the study. In parallel, a modified version of the task was implemented to be carried out in a magnetic resonance study. The entire study involved 1 EEG session, followed by 2 MRI sessions, the acquisition stage of which is concluded. Future MRI analysis may establish further evidence to determine the dynamics of the frontal regions in the verification decision. Although it is also possible that the differentiation of the strategy used is less, by evaluating experienced participants in the task in this instance, the behavior may present the tendency to the integrative strategy, as it represents the strategy with the most efficient use of information. The EEG study determined the bases for the MRI study that aims to complement the results in both humans and monkeys (Stoll, et al., 2016). With twice the

number of sessions and greater spatial resolution, the aim is to clarify the results raised in this thesis.

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“No man is brave that has never walked a hundred miles. If you want to know the truth of who you are, walk until not a person knows your name. Travel is the great leveler, the great teacher, bitter as medicine, crueler than mirror-glass. A long stretch of road will teach you more about yourself than a hundred years of quiet.”

The Name of the Wind, Patrick Rothfuss