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Reward and motivational processes during performance monitoring: a psychophysiological approach.

Davide Gheza

Supervisor: Prof. Dr. Gilles Pourtois
Co-supervisor: Prof. Dr. Chris Baeken

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Guidance Committee

Prof. Dr. Gilles Pourtois (promotor)
Department of Experimental Clinical and Health Psychology, Ghent University.

Prof Dr. Chris Baeken, (co-promotor)
Department of Psychiatry and Medical Psychology, Universitair Ziekenhuis, Ghent, Belgium.

Prof. Dr. Rudi De Raedt,
Department of Experimental Clinical and Health Psychology, Ghent University.

Prof. Dr. Daniele Marinazzo,
Department of Data Analysis, Ghent University.

Dr. Antonio Schettino
Department of Experimental Clinical and Health Psychology, Ghent University.

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Chapter 1: Background and thesis aims

1. Reward And Motivation

In this first section we introduce the psychological constructs of reward and motivation, and the associated broad areas of psychological research of higher relevance for the present thesis. We draw attention to some of the classical psychological and neurophysiological models that have been proposed in the field to account for their role and expression in human cognition and behavior. For each of these two macroscopic constructs, we outline their relevance for psychopathology research, with an emphasis on internalizing disorders, and more specifically unipolar major depression.

1.1. Reward: relevance in human cognition, behavior, and health.

Reward is associated with the subjective experience of pleasure, or elevated hedonic tone. Hedonia (Ancient Greek: ἡδονή) corresponds to a state of pleasure or enjoyment. Together with eudemonia (experience of a valuable and meaningful life), the capacity for pleasure is thought to be a necessary component of well-being, happiness, and mental health (Berridge & Kringelbach, 2011, 2015). Rewarding events trigger specific physiological and brain responses that have been shaped by evolution and are shared across species, serving to motivate an organism to pursue its needs and environmental fitness (Berridge & Kringelbach, 2015).

1.1.1. The reward system.

Reward is not a unitary or monolithic process. Recent advances in the neuroscientific study of reward processing put forward the notion of distinct psychological components, with partly non-overlapping neural representations. Specifically, the brain reward system encompasses three sub-components of liking, wanting, and learning (Berridge & Robinson, 1998, 2003). Liking, also termed consummatory pleasure, is the “purest”

affective component of reward, and corresponds to the hedonic impact of a stimulus. The elective way of measuring objective hedonic reaction is the taste-reactivity paradigm, where subjects (either animal models or humans) are exposed with sensorial stimuli (e.g., sucrose solutions or pleasant smell), and their liking reaction is assessed by means of registering affective face expressions, self-report scales, or behavioral choices between stimuli indicating preference. The ventral striatum is a core forebrain structure of the liking sub-system. Hedonic liking reactions are mediated by neural events in small hedonic hotspots, such as opioid-dependent activity in the shell region of the nucleus accumbens (Nacc), and in the ventral pallidum (Berridge & Kringelbach, 2015; Berridge & Robinson, 2003). Wanting, in turn, refers to the motivational component of reward processing. It corresponds to, and is often referred as, the anticipatory, appetitive, or approach phase of motivated behavior. Wanting is predominantly mediated by the dopaminergic mesolimbic pathway, including dopaminergic projections form the ventral tegmental area (VTA) and substantia nigra (SN) to the ventral striatum (Knutson, Adams, Fong, & Hommer, 2001; Knutson & Greer, 2008). According to the incentive salience hypothesis (Berridge & Robinson, 1998), dopamine (DA) mediates selectively the wanting component of reward, by transforming the 'cold' representation of a (conditioned) stimulus into an attractive incentive capable of 'grabbing attention' on the one hand, and for which the animal is willing to work on the other. In fact, although a stimulus that is liked is often concurrently wanted, experimental manipulation of DA (e.g., DA depletion) impacts primarily on motivated behavior, including activation, approach or reward seeking, and effort exertion (Salamone & Correa, 2012), but not necessarily on the "liking" reactions (Salamone, Cousins, & Bucher, 1994). Conversely, in several forms of addiction, we can observe a clear impact of the DA-mediated wanting system on behavior (e.g., craving and compulsion), with low or absent experience of liking (Incentive-Sensitization Theory; Robinson & Berridge, 1993;

Volkow, Fowler, Wang, Swanson, & Telang, 2007). Finally, learning refers to developing stimulus-stimulus and stimulus-response associations (Pavlovian conditioning) or response reinforcement (instrumental conditioning). Neural substrates of these processes are widely distributed across subcortical and cortical structures and, according to the incentive salience hypothesis, can be parsed from those implied in wanting (Berridge & O'Doherty, 2013; Berridge, Robinson, & Aldridge, 2009). For instance, mesolimbic activation in rats seems to mediate incentive coding more than prediction signal coding in the ventral pallidum (Tindell, Berridge, Zhang, Peciña, & Aldridge, 2005), hence the reward-predicting value of a learned conditioned stimulus can be dissociated from its motivational (DA-dependent) value (Berridge et al., 2009; J. Zhang, Berridge, Tindell, Smith, & Aldridge, 2009). Yet, mesolimbic incentive salience might contribute to and boost reinforcement learning by increasing wanting for conditioned and unconditioned stimuli (Berridge & Robinson, 2003; see also Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006). To note, other authors disagree with this view, stating instead a fundamental role of VTA dopaminergic activity in reinforcement learning by signaling reward prediction errors (Berridge & O'Doherty, 2013; Fiorillo, Tobler, & Schultz, 2003; Schultz, Dayan, & Montague, 1997).

Another important concept pertains the distinction between (implicit) associative learning discussed so far, and cognitive learning. The latter is more complex than the former, and implies (conscious) encoding of multiple relationship between stimuli and actions, its products are declarative memories guiding goal-directed actions, and relies heavily on broader prefrontal cortical (PFC) networks. In a similar vein, conscious hedonic feelings and explicit cognitive goals could constitute the explicit counterpart of liking and wanting. Many PFC structures respond to, and regulate, reward processing (Haber & Knutson, 2010; Rolls, 2000). Among them, the ventro-medial portion (vmPFC) seems to be involved in processing abstract rewards and the subjective value of stimuli, and the

value signal encoded in the vmPFC may drive goal-directed decisions (Hare, Camerer, & Rangel, 2009). Similarly, secondary rewards (e.g., money) activate the most anterior region of the orbital frontal cortex (OFC), while the posterior region seems more sensitive to primary rewards (e.g., food and erotic stimuli) (Sescousse, Caldú, Segura, & Dreher, 2013). The OFC is also critical for storing stimulus-reinforcement association for both positive and negative reinforcers, and for behavioral adaptations after changes in action-outcome contingencies (Kringelbach & Rolls, 2004). Primary and secondary rewards also reliably activate the bilateral anterior insula, endowing this region not only with a role in interoception, but possibly also in the affective experience and awareness of non-bodily stimuli such as rewards (Sescousse et al., 2013). Finally, the dorsal anterior cingulate cortex (dACC) and the dorsal prefrontal cortex (dPFC) are thought to implement complementary processes for motivated and goal-directed behavior, including monitoring, comparing, and selecting valued options (Haber & Knutson, 2010; see also section 2.3). In sum, the reward system entails a distributed network of subcortical and cortical regions that are heavily interconnected with each other, and that ultimately allows for adaptive behavior in mammals who are confronted with a complex and ever-changing environment. Reward and motivational information are integrated with higher-level processes, such as decision-making, action planning, and cognitive control, that are more heavily represented in the PFC.

1.1.2. Reward in anhedonic populations.

In the last three decades, there has been a surge of studies on affective, behavioral, and neural responses to stimuli endowed with reward or positive affect properties. This was partially motivated by the assumption that impairment in this domain (e.g., liking) could account for the etiology and maintenance of a range of psychiatric disorders

characterized by anhedonia. Anhedonia has been traditionally defined as the loss of pleasure or lack of reactivity to pleasurable stimuli (American Psychiatric Association, 2000). This definition encompasses an articulated range of symptoms that play a role in depression disorders, schizophrenia, substance use disorders, Parkinson's disorder, and others. As such, anhedonia has been put forward as a potential endophenotype of these disorders, and Major Depression in particular (MDD; Gorwood, 2008; Hasler, Drevets, Manji, & Charney, 2004). The concept of endophenotype was introduced to aid the decomposition of diseases with complex genetics (including psychiatric disorders), and refers to an internal phenotype component situated along the pathway between genotype and disease (Gottesman & Gould, 2003). With regard to MDD, it has been proposed that the intermediate phenotypic expression of anhedonia may arise from a detrimental effect of stress on mesocorticolimbic DA pathways (Pizzagalli, 2014), thus mediating between biological vulnerability/genetic makeup, environmental factors (e.g. stressors), and the final outburst of heterogeneous pathophysiological manifestations.

In recent years a more refined conceptualization of anhedonia benefitted from the theoretical and neurobiological demarcation of the distinct components of reward processing (Admon & Pizzagalli, 2015; Rizvi, Pizzagalli, Sproule, & Kennedy, 2016; Thomsen, 2015; Treadway & Zald, 2011), as briefly outlined above (see section 1.1.1.). Assuming MDD as a case study, little evidence supported the traditional view assuming a core loss of "pleasure", or liking reactions per se, in this disorder. In particular, studies adopting taste-reactivity paradigm failed to show clear differences between MDD patients and healthy controls in hedonic reactivity to sweet solutions (Berlin, Givry-Steiner, Lecrubier, & Puech, 1998; Dichter, Smoski, Kampov-Polevoy, Gallop, & Garbutt, 2010). Similarly, experimental paradigms using positive cues to elicit affective and behavioral responses often found mixed results (for a review, see Pizzagalli, 2014). Instead, anhedonia in MDD is more clearly reflected in

reduced willingness to exert effort to gain reward (Treadway, Bossaller, Shelton, & Zald, 2012), or in a dissociation between spared reward liking and impaired motivation, expressed as lack of selective effort expenditure for the liked objects (Sherdell, Waugh, & Gotlib, 2012). Altogether, these studies pointed to a cardinal role of anticipatory anhedonia (i.e., wanting component of reward) over consummatory pleasure in MDD. Moreover, some evidence also highlighted dysfunctions of (implicit) reward learning in MDD. First, in a probabilistic reward task requiring discrimination between asymmetrically reinforced stimuli, MDD compared to controls showed a reduced ability to develop a response bias toward more rewarded cue over the course of several trials, hence to modulate behavior as a function of reinforcement history (Pizzagalli, Iosifescu, Hallett, Ratner, & Fava, 2008; Vrieze et al., 2013). Second, in an study adopting a probabilistic reinforcement learning task, individuals with current or past MDD showed a bias toward learning from punishment as compared to rewards, with punishment feedback (FB) being also associated with larger error signal amplitude at the EEG level (Cavanagh, Bismark, Frank, & Allen, 2011). We come back to the EEG correlates of reward processing in section 2.2. below.

To note, despite mixed findings at the behavioral level, impairments in reward sensitivity are well documented at the neural level. For instance, using the Monetary Incentive Delay task (Knutson, Westdorp, Kaiser, & Hommer, 2000), Wacker et al. (Wacker, Dillon, & Pizzagalli, 2009) found that anhedonia in MDD patients correlated positively with reduced striatal (NAcc) activity in response to reward, and increased resting activity in the rostral ACC. At the electrophysiological level, a vast literature documented reduced reward sensitivity for MDD patients in response to monetary FB, as reflected in the modulation of the Reward Positivity component of the electroencephalogram (Moran, Schroder, Kneip, & Moser, 2017; Proudfit, 2015) (See also section 2.2.2). A review of the literature on the neural substrates of anhedonia has been done elsewhere and is going beyond

the scope of the present thesis (Keren et al., 2018; B. Zhang et al., 2016). However, it is noteworthy that these reviews emphasize that more work is needed to clarify the correspondence between neural signs of anhedonia emerging from a multitude of experimental paradigms, and the corresponding component of anticipatory vs. consummatory reward processing.

1.2. Motivation: what's in a name.

The cursor line blinks at the beginning of this row, pushed forward by these stunted words. Do I want to write this section? Am I driven by the intrinsic motivation of giving shape to blurred ideas into a coherent bit of information? Do I anticipate the pleasant feeling of satisfaction from having it eventually done? Or am I mostly driven by the fearful consequences of pushing the deadline? As we briefly outline below in this section, the psychological mechanisms behind goal-directed behavior in humans revolve around many explanatory variables, including the expected reward of this endeavor (both intrinsic and extrinsic), the cost and risk associated with it, the environmental factors in which this behavior is performed (e.g., controllability of events), as well as personality characteristics and the genetic makeup. More broadly, in psychological research there is not such a thing as a univocal construct of "motivation". Rather, the term is used in a range of (mostly operational) definitions, in association either with cognitive or affective dimensions. Often, it is simply an attribute describing the quality of other processes or functions (e.g., motivated or goal-directed behavior).

An interesting dichotomy between different types of motivation processes has been proposed within the Self-Determination Theory (Ryan & Deci, 2000), based on different "motives" or goals that support actions. These authors observed that humans, in their healthiest state, are curious and inquisitive creatures, prone to learning by means of spontaneous

exploratory behavior. Doing an activity for its inherent satisfaction correspond to intrinsic motivation: for this form of motivation, the activity per-se is rewarding, and provide satisfaction for psychological needs such as competence, autonomy, and relatedness. On the other hand, extrinsic motivation pertains to an action driven by a separable outcome, or instrumental value (yet, with a varying degree of personal endorsement and action valuation, as opposed to a purely externally controlled action). These concepts are worth to be considered when operationalizing motivation in the experimental setting, where task characteristics and personality features can for instance impact on levels of task engagement and performance, reward sensitivity, and cost-benefit decision making.

Another influential conceptualization of motivation comes from the work of Gray (1990), and bridges personality psychology with early neuropsychological work. He proposed the existence of three fundamental brain systems, mediating both emotion and cognition in the mammalian brain: a behavioral approach system (BAS), a fight-flight system (FFS), and a behavioral inhibition system (BIS). In this framework, emotional states (and their representation in the specific brain subsystem) are elicited by reinforcing stimuli (either appetitive or aversive), that can then serve as goals for instrumental learning (e.g., to escape a threatening stimulus). Of particular interest for the scope of this work, BIS reflects sensitivity to punishment and avoidance motivation, whereas BAS is associated with reward sensitivity and approach motivation. Moreover, these two systems, that are somehow independent from each other, proved to account for individual differences in personality dimensions and affect style (i.e., sensitivity to punishment or reward, and consequent aversive or appetitive motivation). This conceptual framework led to the validation of a scale for the assessment of dispositional BIS and BAS sensitivities (Carver & White, 1994). Eventually, similar systems of affective style (approach and withdrawal motivation systems) were proposed by Davidson (Davidson, 1998). Their brain correlates were

hypothesized to bear on asymmetric prefrontal cortex activity (Davidson, 1992), and to hold diagnostic power for vulnerability to mood and anxiety disorders (Henriques & Davidson, 1991; Thibodeau, Jorgensen, & Kim, 2006; but see: van der Vinne, Vollebregt, van Putten, & Arns, 2017).

1.2.1. Dopamine and motivation.

As outlined above in the previous sections, the DA neuromodulator system is primarily involved in motivational aspects of reward processing. One influential line of research showed that mesencephalic DA neuron firing is consistent with a signal reflecting prediction error for reward (Schultz et al., 1997). These neurons respond to the receipt of various forms of rewarding stimuli, but also to unexpected deviations between the actual occurrence of reward and predictions about time and magnitude of reward, in line with a temporal difference reinforcement learning algorithm. Moreover, these neurons project to brain areas concerned with motivation and goal-directed behavior, including striatum and frontal cortex. Second, according to the incentive salience hypothesis (Berridge & Robinson, 1998), interfering with DA transmission does not impact on the hedonic evaluation of reinforcers (including consummation of available rewards), nor learning of new stimulus values or action-outcome associations, but rather on attribution of incentive salience (the motivational “wanting”) to neural representation of valued stimuli. Third, Salamone and colleagues (Salamone et al., 1994) showed that Nacc DA depletions interfere with the ability to mobilize effort to obtain reward, producing low-effort/low-reward bias in effort-based choice tasks, while the opposite bias is obtained with DA enhancing drugs (Salamone, Correa, Yang, Rotolo, & Presby, 2018). They argued that DA mediates both appetitive and aversive motivational processes, and particularly the energizing and effort-dependent aspects of stimuli (Salamone & Correa, 2012).

All these perspectives converge and entail fundamental functions of DA in approach motivation, and in developing behavioral policies in general. Such motivational influences of DA on behavior may be result of direct biasing cost-benefit decition making (Salamone et al., 2018), incentive salience attributions (Berridge et al., 2009), or modulation of the magnitude of reward prediction errors, that in turn influences instrumental learning and decision policies (Pessiglione et al., 2006). All of these processes have potential implications on the pathophysiology of anhedonic symptoms. In fact, hyper- or hypo- regulation of this 'wanting' neural system is thought to play a causal role in the etiology and maintenance of psychiatric disorders characterized by motivational deficits, including major depression, Parkinson disease, addiction (e.g. substance abuse), and pathological gambling (Zald & Treadway, 2017).

1.2.2. Motivation: integration of expected reward and cost.

These lines of fundamental research in neuroscience inspired a reformulation of theoretical models of anhedonia in psychiatric disorders, and depression in particular (Thomsen, 2015). Recently, the centrality of anhedonia as lack of pleasure or reactivity to pleasurable stimuli has been superseded by an explicit focus on motivation, operationalized as the cost that a subject would accept in order to achieve a goal or attain a benefit (Pessiglione, Vinckier, Bouret, Daunizeau, & Le Bouc, 2018). In this new framework, couched in decision theory, motivation is the function that orients and activates the behavior according to a goal identity and to its value, and is traded-off by the expected cost of behavior. Consistent with a new emphasis on motivation as behavioral activation and effort exertion, Treadway (Treadway & Zald, 2011) introduced the term "decisional anhedonia", referring to specific alteration in cost-benefit decision making in MDD. Specific impairments in effort-based decision making have been shown in a study adopting the Effort Expenditure for Reward task

(Treadway, Bossaller, et al., 2012), where MDD patients were less willing to expend effort for reward compared to healthy controls. DA activity in striatum and vmPFC correlated with the willingness to expend greater effort for larger rewards in healthy volunteers (Treadway, Buckholtz, et al., 2012). A complementary impairment in reward-based decision making was found with a probabilistic learning task, where MDD patients showed a diminished tendency to base decisions on reward, but not on punishment likelihood (Kunisato et al., 2012).

Physical effort, as implemented in the Treadway task, is not the only form of cost on which humans are called to operate decisions. Cognitive effort also evokes avoidance behavior (Kool, McGuire, Rosen, & Botvinick, 2010), biasing cost-benefit decision making towards reward devaluation (Apps, Grima, Manohar, & Husain, 2015). Interestingly, a cost-benefit mechanism has been recently integrated in a theoretical model of cognitive control, the latter being conceived as a form of cognitive effort (Shenhav, Botvinick, & Cohen, 2013). According to this model, the allocation of cognitive control depends on a trade-off between the expected payoff of the controlled process, the amount of control required, and the cost in terms of cognitive effort. As discussed more extensively in the following sections, several other theoretical models of effortful control operationalize motivation as control allocation, assuming a pivotal role of the ACC (Vassena, Holroyd, & Alexander, 2017). Advances in this direction may prove particularly useful for explaining cognitive control deficit in MDD (Grahek, Everaert, Krebs, & Koster, 2018).

2. Electrophysiology Of Performance Monitoring

In this section we introduce the theoretical and methodological background of the thesis. We start with delineating basic notions behind the study of electrical brain activity, as achieved using electroencephalography (EEG). We then move to the concept of performance monitoring, integrating the research traditions from experimental and translational fields. We summarize the main empirical contribution of electrophysiology research on the current understanding of the cognitive and neural mechanisms underlying performance monitoring. We finally narrow down our focus on the electrophysiology of performance monitoring during external feedback presentation. Finally, we show how empirical evidence informed theoretical models accounting for the neurophysiological mechanism of reward processing, reinforcement learning, and cognitive control allocation.

2.1. Electroencephalography.

2.1.1. Foundation principles.

The study of the electric activity of the human brain dates back to ninety years ago, when Hans Berger (1929) first reported rhythmic voltage changes in the signal recorded and amplified from electrodes placed on the scalp (electroencephalogram – EEG). This oscillatory electric potential reflects the contributions of several cellular processes within a volume of brain tissue. The main contributions are excitatory and inhibitory postsynaptic transmembrane currents (ionic flux between the intra- and extracellular space), that generate a phasic electric dipole between the apical dendrites and the cell body (Buzsáki, Anastassiou, & Koch, 2012). These relatively slow events (synaptic currents), lasting tens to hundreds of milliseconds, can overlap in time between individual neurons. As neural activity becomes synchronous across thousands of neurons, their electric

dipoles superimpose (particularly for ensembles of pyramidal neurons with parallel geometric orientation), generating an electric field strong enough to travel through brain tissue, meninges, skull and scalp. This potential is influenced by the spatial alignment of neurons in a given brain source, by the geometry of the brain tissue (e.g., folding of the cortex), scales as inverse function of the distance between the source and the recording site, and is distorted by the varying resistivity and shape of the tissues that it crosses. For this reason, together with other micro- and mesoscopic level effects (including spatial averaging between different sources, and the respective level of synchrony of their neural populations), the scalp-level activity that can be measured with respect to a reference potential (i.e., the EEG) has little relationship with firing patterns of individual neurons. Instead, it reflects mainly the smoothed and macroscopic effects of synchronized fluctuations of large assemblies of spatially aligned neurons, with stronger contributions from cortical areas close to the scalp (Buzsáki et al., 2012; Cohen, 2014; Kappenman & Luck, 2012).

As a result, the raw EEG reflects the combination of hundreds of neural sources of activity (Luck, 2005). Nevertheless, according to the traditional electrophysiological approach, neural responses associated with specific neuro-cognitive events can emerge distinctively from the ongoing background activity. Specifically, a large voltage fluctuation in the EEG that are time-locked to a specific event (either external, as a sensory stimulus, or internal, as a motor response) is defined as event-related potential (ERP). ERPs that are characterized by large deflections can sometimes be seen on the single trial level. However, the most common analytic approach to ERPs consist in segmenting the EEG data, aligning single trials according to the onset of the event of interest, and averaging them – hence retaining the activity "shared" across trials and removing the noise, which is by definition random activity across them. Thus, an implicit assumption of ERP research is that background activity (i.e., non-time-locked), as well as activity that is not coherent in phase across trials (i.e.,

non-phase-locked), is not informative about the neuro-cognitive processes underlying the EEG at the onset of the event. The resulting ERP waveform appears on the scalp as a series of positive and negative peaks, that vary in polarity, amplitude, latency, and scalp distribution (i.e. topography). A second fundamental assumption of ERP research is that the ERP waveform can be separated into different components, that are the portions of the scalp recorded activity generated by "discrete intracranial sources of voltage that reflect specific neurocognitive processes" (Kappenman & Luck, 2012). Importantly, the positive and negative polarity peaks, temporally spaced after the eliciting event, are not to be univocally associated to single ERP components. This is mainly because a varying number of simultaneously active sources contributes to some extent to the ERP at any given scalp location, and because even neural activations associated with temporally distinct mental process (i.e., components) can persist for hundreds of milliseconds, and hence overlap in the ERP waveform (superposition problem). Given these constrains, the task of the experimenter is to identify the conditions that modulate the expected features of a specific component, including polarity, latency, topography, and sensitivity to the experimental manipulation tapping on the function under scrutiny (Donchin, Ritter, & McCallum, 1978). Converging evidence from each of these features, together with the specificity of a given component's properties for the cognitive process of interest, should be a requirement for a component's identification and scoring (Kappenman & Luck, 2012), and more generally for subsequently applying the ERP analysis to answer psychological and neurocognitive questions.

2.1.2. Evoked and induced signals.

Notably, after the trial-averaging procedure for the identification of ERPs, the EEG activity that is retained is both time-locked and phase-locked to the event of interest. In other words, by definition the ERPs

represent the subset of EEG data that, across trials, is coherent in phase at the onset of the event (time = 0). Conversely, time/frequency estimation methods allow to quantify the total task-related activity (including phase-locked and non-phase locked) in terms of power changes in any given frequency, before trial-aggregate is eventually computed (Cohen, 2014). Hence, in addition to provide a quantitatively richer signal in terms of signal-to-noise ratio, time/frequency analysis of EEG activity has some advantages over ERP analyses. First, assessing the task-related EEG activity in terms of frequency-specific power is free from the assumption that only phase-locked activity is cognitively relevant, as entailed by a classical ERP approach (see section 2.1.1. above). Second, parsing phase-locked from non-phase locked activity allows to some extent to draw a distinction between temporally discrete neural event (what is usually assumed to reflect an ERP component) from more plausible oscillatory activity endowed with specific functional properties. In fact, several authors contend that non-phase-locked activity constitutes stronger evidence for the presence of oscillations (Cohen & Donner, 2013; Donner & Siegel, 2011; Tallon-Baudry & Bertrand, 1999). In particular, non-phase-locked spectral power change is often observed during higher cognitive processes, including top-down attention, decision-making, and other integrative functions that rely on intrinsic network interaction and transient connectivity within the brain (Siegel, Donner, & Engel, 2012), rather than merely on external input. In this context, long-range cortical interactions may be mediated by oscillation patterns in relatively low frequencies (from Beta to Theta) (Donner & Siegel, 2011), possibly through a mechanism of interregional oscillatory synchronization (coupling). This mechanism is defined as “binding” (Singer & Gray, 1995), indicating that synchronous firing patterns in neural subpopulation may entrain and induce the firing of neighboring subpopulation, particularly when they participate in encoding related information. This process can also give rise to a synchronization chain that can travel across space, as

recently evidenced for Beta and Theta frequency oscillations (H. Zhang, Watrous, Patel, & Jacobs, 2018), and that may support brain connectivity and large-scale coordination (Smith et al., 2015). Even at the local level, neural oscillations, and specifically rhythmic synchronization within an activated neuronal group, have been proposed to have a central role in cognition. According to the Communication through Coherence hypothesis (Fries, 2015), neural synchronization has a causal role on (local) neural communication, on top of the structural anatomical connectivity. More specifically, rhythmicity of neural activity involves cycles of excitation and inhibition of the neurons. Crucially, the sensitivity to their synaptic input (from pre-synaptic neurons) would be modulated according to the cycle phase. Thus, effective communication between neuronal groups would depend on their oscillatory coherence. In turn, changes in synchronization would also alter the effective communication.

In sum, evoked and induced oscillations differ in their phase-relationship to the eliciting stimulus. In the time-frequency domain, evoked (i.e., phase-locked) activity is obtained by averaging the signal over trials (i.e., the ERP), and subsequently computing time-frequency analysis. Induced activity (i.e., non-phase-locked) is obtained by first applying time-frequency decomposition to each trial, averaging across single-trials power (obtaining the total power), and finally subtracting the evoked activity. Commonly, it is assumed that evoked oscillations reflect the stimulus-locked ERP spectrum, while induced oscillations reflect intrinsic higher-order processes. To note, such a sharp distinction between the mechanisms underlying evoked and induced responses, being associated respectively to externally (dynamic) or internally (structural) driven effects, has been challenged by modelling neuronal interactions (David, Kilner, & Friston, 2006). More generally, the extent to which electrical fields are causally involved in cognition is still under debate (Cohen, 2014; Fries, 2015), and despite the evidence and theoretical accounts (partly) reviewed here, it might still be the case that spatiotemporal field fluctuations in the

brain are mostly an epiphenomenon of neuronal activity (Buzsáki et al., 2012). Nevertheless, this would not lessen the heuristic power of electrophysiology in the study of specific brain functions, including performance monitoring that lies at the heart of this thesis.

2.2. Performance monitoring: reward processing and cognitive control mechanisms.

"The anterior cingulate cortex is the grave of the cognitive neuroscientist". This witty remark, overheard during my first symposium on Motivation and Cognitive Control (St. Andrews, 2016), was picked up by my performance monitoring system as a daunting error signal. A mismatch, or prediction error, occurred between the expected and the observed value of my freshly chosen research field. Evidently, some tragic reappraisal might have followed.

Which facial mimicry did I just elicit in the reader? Did the sarcasm come through? We are constantly vigilant for internal or external signals regarding the adequacy of our actions with respect to the intended goal, that can be proximal or more distal. For any form of willed and goal-oriented behavior - from typing these words, to embracing a long-term career path - monitoring the ongoing performance is a requisite to keep on the expected and desired track. Performance monitoring (PM) allows the agent to promptly detect any possible divergence from the planned interaction with the environment. A common example are mistakes (mis-take: take in error), undesired outcomes of the agent's behavior, whose detection by PM usually triggers the need for increased control, and eventually behavioral adjustment meant to lower their probability of reoccurrence in the future. Inadequate behavioral responses (i.e., errors) may arise also from sudden changes in the context, whereby an automatized response may no longer be adequate, for instance. Thus, despite their negative connotation (Aarts, Houwer, & Pourtois, 2012),

errors are an irreplaceable source of information. Their timely detection by PM allows behavioral adaptation, learning, and coping with changes in an uncertain world.

From a cognitive perspective, flexible goal-directed behavior requires a broader range of cognitive functions, including orienting attention and filtering irrelevant information, decision-making, response activation and inhibition, PM, and reward-based learning. These functions are among the main constituents of cognitive control during decision making, and they fuel self-regulation (Ridderinkhof, Van Den Wildenberg, Segalowitz, & Carter, 2004). According to a narrower definition, cognitive control (CC) specifically refers to the ability to guide thoughts and actions according to internal goals (Miller & Cohen, 2001). An influential tri-partite model fractioned CC, also referred to as executive functions (EF), in the high-level cognitive abilities of inhibition (either automatic responses, or distracting information), working memory maintenance or updating, and shifting between task sets (Friedman & Miyake, 2017). However, a current challenge in cognitive neuroscience is to reach a mechanistic understanding of when, how, and with which intensity cognitive control is recruited, at expenses of more automatized and habitual processing. In this framework, PM subsumes precisely the set of cognitive and affective functions detecting the need, type and magnitude of control to be exerted (Ullsperger, Fischer, Nigbur, & Endrass, 2014).

PM is also characterized by an affective dimension, since the effects of our actions are also evaluated along their valence (positive or negative), with respect to the intended goal. The difference between the expected and the actual reward value of actions is defined by reward prediction error (RPE), and is associated with the generation of specific dopamine signals deep in the brain, more specifically in the ventral tegmental area (VTA) and substantia nigra (Schultz et al., 1997; see section 1.2.1.). A vast research in affective neuroscience relied on measuring the behavioral and physiological responses to reward outcomes to unveil the neural

mechanism of reward processing (Berridge & Kringelbach, 2015), as briefly reviewed in section 1.1. Clinical and translational neuroscience benefitted from the advances in this field to investigate the etiology of disorders characterized by abnormal reward processing (anhedonia) and motivation, including depression disorders and schizophrenia (Admon & Pizzagalli, 2015; Barch, Pagliaccio, & Luking, 2016).

In the following sections, we briefly review the literature about PM with a specific focus on electrophysiology/EEG research. Investigating the scalp-level electric activity of the brain during PM offers a unique window onto the time-resolved neurophysiological mechanisms of both cognitive control and reward processing (e.g., when and how a rewarding feedback is elaborated, with a precision of milliseconds from the onset of its presentation). Although it is artificial to draw a net distinction between cognitive and affective mechanisms underlying PM, as well as their motivational influences on behavior, these categories are more or less consistent with the traditional demarcation between experimental/cognitive and affective/clinical research fields, and the corresponding interpretations of the EEG components elicited at the scalp level during PM.

2.2.1. Temporal dynamics of PM: anticipation, response, feedback.

As mentioned in the previous section, PM is functional to detecting the need for controlled processing, in service of performance optimization. During goal-directed behavior, PM is a core node in a feedback-loop in which the difference between expected and actual action outcomes is used recursively to update the action value, refine outcome expectations (i.e., learning the action-outcome contingency), and inform response adjustments (Ullsperger, Danielmeier, & Jocham, 2014). PM is specifically in charge of detecting these mismatches between predicted and observed

action value, and works continuously throughout action anticipation, response selection, and feedback (FB) processing.

At the EEG level, a sequence of ERPs is associated with PM, sharing a rather uniform structure across these stages (anticipation, response, FB). This sequence starts with an early negativity-positivity complex, observed on fronto-central scalp electrodes, and continues later with a sustained parietal positivity (Ullsperger, Fischer, et al., 2014). Depending on the processing stage (i.e., time-locking event) and the experimental task, each component of this ERP complex is referred to with a specific label.

When the ERP activity is time-locked to stimulus presentation (response anticipation), the early fronto-central negative deflection peaking between 200-300ms after stimulus onset is referred to as N2, and has been associated to the required difficulty of a response (i.e., action cost), in particular during response conflict. In fact, increased fronto-central N2 amplitude is thought to be related to conflict detection during the simultaneous activation of competing response representations (Van Veen & Carter, 2002). Similarly, the N2 is increased for stimuli mandating response inhibition in Go/Nogo and Stop signal tasks (Donkers & Van Boxtel, 2004; Enriquez-Geppert, Konrad, Pantev, & Huster, 2010). Besides control-related activity (e.g., reflecting response conflict or task engagement), the N2 component modulation also reflects attention-related effects such as surprise (e.g., orienting to novel stimuli) and mismatch from attended perceptual stimuli (Folstein & Van Petten, 2008). Following the N2, a fronto-central P3a and a parietal P3b complete the prototypical ERP complex (Ullsperger, Fischer, et al., 2014).

At the response level, a rich research tradition focused on the modulation of the first fronto-central negative deflection in relation to response accuracy. An error-related ERP activity was first observed in the 1990s using a speeded-choice reaction time task, and called error

negativity (Ne) (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1990; Gehring, Goss, Coles, Meyer, & Donchin, 1993). This negative deflection, also known as error-related negativity (ERN), arises early after incorrect response and peaks within the first 100ms on fronto-central sites. This component can be observed typically in reaction time tasks with fixed stimulus-response mappings (e.g., Go/Nogo and Eriksen flanker tasks), as well as in other paradigms where the accuracy of the response can be immediately evaluated (e.g., the late phase in reinforcement learning tasks, dominated by high response accuracy). Accordingly, it is thought to reflect the comparison process between the representation of the actual and the required response (Falkenstein, Christ, Hohnsbein, & Sussman, 2000). Following the Ne/ERN, a fronto-central error positivity (Pe) and a parietal late Pe likely reflect later aspects of error processing, including the conscious appraisal of response errors and/or the processing of the enhanced motivational significance of these "special" events (Ridderinkhof, Ramautar, & Wijnen, 2009).

At the FB level, a similar sequence of events is usually observed when PM relies on external source of information to gauge action's value. This can be achieved with experimental paradigms in which the response selection happens under uncertainty, as in time-estimation (Miltner, Braun, & Coles, 1997), gambling (Hajcak, Holroyd, Moser, & Simons, 2005), and reinforcement learning tasks (Eppinger, Kray, Mock, & Mecklinger, 2008). The corresponding fronto-central negative deflection, called feedback related negativity (FRN), peaks between 200-300ms after FB onset, and is larger for incorrect than correct FB, as well as for unexpected compared to expected outcomes. Following this negativity, a fronto-central P3a and parietal P3b is commonly observed.

In sum, at different stages of PM, ranging from anticipation to production and subsequent evaluation, negative ERP components (N2, ERN, and FRN) are elicited that seem to be somehow functionally and morphologically related. The proposal that a common and temporally

uniform ERP complex across the different stages of PM reflects a shared neural mechanism is also supported by source localization (Gruendler, Ullsperger, & Huster, 2011), indicating that this family of components (N2, ERN, and FRN) originate from an overlapping neural source in the dorsal compartment of the anterior cingulate cortex (ACC – for some authors extending to the broader anterior midcingulate cortex, or rostral cingulate zone) (Debener, 2005; Hauser et al., 2013; Wessel, Danielmeier, Morton, & Ullsperger, 2012). The ACC, being involved in processing novel/unexpected events, response conflict and errors, and negative FB, represents a core hub in the PM network implied in signaling the necessity of control and adaptation, by interacting with areas involved in motor, cognitive, and possibly motivational functions (Ridderinkhof, Ullsperger, & Nieuwenhuis, 2004).

2.2.2. FB processing: FRN / RewP component.

In many real-life situations, often characterized by low information about the circumstances and possible consequences of our actions, an exploratory behavior is required. By trial and error, we cautiously probe action's accuracy with respect to the intended goal, and we monitor its consequences mostly based on external FB. Scrutinizing electrophysiological responses to FB in situation of high action-outcome uncertainty allows to gauge the strongest reactions of PM to the need of increased control, as well as along the hedonic dimension of reward processing.

2.2.2.1. Reward and expectancy.

As mentioned in the previous section, the FRN is one of the earliest and main electrophysiological correlates of PM during FB processing (Miltner et al., 1997). It corresponds to a phasic negative fronto-central

ERP deflection peaking around 250 ms after negative FB onset. Miltner and colleagues (1997) first identified this component using a time-estimation task. This ERP component was increased for FB indicating incorrect performance independently from the sensory modality with which the FB was presented. Moreover, it showed morphological characteristics similar to those of the ERN, and was therefore proposed to manifest (together with the ERN) the activity of a generic error detection system. The FRN component can be also observed in gambling tasks (Gehring & Willoughby, 2002; Hajcak, Moser, Holroyd, & Simons, 2007; Holroyd, Nieuwenhuis, Yeung, & Cohen, 2003), as well as in reinforcement learning tasks (Eppinger et al., 2008; Holroyd & Coles, 2002).

The psychophysiology literature has witnessed an intense debate regarding which features of the FB eventually determine the amplitude modulation of this specific ERP component. A first object of debate concerned whether the FRN is sensitive to response accuracy as compared to reward attainment. In particular, in a seminal study, Gehring and Willoughby (2002) challenged the assumption that the FRN reflects purely error detection, but rather the evaluation of the motivational impact of events. Adopting a two-alternatives gambling task, Gehring and Willoughby (2002) showed that the FRN can differentiate the actual monetary outcome (gains versus losses), no matter the relative value of the not selected alternative being better or worse (i.e., response accuracy). A solution to this debate came from a study showing that both performance (accuracy of response) and utilitarian value (e.g., monetary reward) can reliably modulate FRN amplitude, depending on which aspect is made more salient in the experimental manipulation (Nieuwenhuis, Yeung, Holroyd, Schurger, & Cohen, 2004). Here on, we use the wording “positive” and “negative” outcome to refer inclusively to these valence dimensions. Interestingly, in addition to being typically larger for negative compared to positive outcome, a wealth of studies reported the sensitivity of the FRN to the expectancy of the outcome. In other words, the FRN

seems to reflect a neural mechanism that weights the magnitude of reward by the likelihood of its attainment (Sambrook & Goslin, 2015). In the latter formulation, the two levels of FB valence typically manipulated - correct vs incorrect FB, or reward vs no-reward - can be conceived as the boundary cases of the continuous variable “reward magnitude”. On the opposite side of the debate, some authors proposed that the FRN foremost reflects expectancy violations, or (unsigned) salience prediction errors, irrespective of the FB valence. First, a clear and similar FRN amplitude was reported for both positive and negative unexpected FB in a study adopting a time estimation task (Ferdinand, Mecklinger, Kray, & Gehring, 2012). Notably, in this experimental design, the authors controlled for the relative frequency of the FB (fixed at 20%, for both positive or negative) applying an adaptive procedure on individual accuracy thresholds. Critically, the authors assumed that matched FB frequency translated equal FB expectancy for the two types of FB. A potential caveat in this study is that, despite their equal frequency, negative FB after extreme responses (very early or very late) may have been more predictable, compared to positive FB after very accurate responses. Ultimately, a confound in (subjective) FB expectancy might also account for the lack of apparent difference of the ERP complex between positive and negative FB. Second, evidence in support of the unsigned prediction error account derived from a study that showed increased FRN amplitude associated with large violations of participant’s expectancies about their own performance (no matter their accuracy in the instructed task; Oliveira, McDonald, & Goodman, 2007), and from another one that surprisingly found increased FRN for unexpected pain omission (what is expected to be a positive outcome; Talmi, Atkinson, & El-Deredy, 2013). However, it could be argued that in these last two studies the accuracy of the subjective prediction of the FB may have inherited higher value or significance than the actual direction of the FB valence (the instructed task goal). In other words, in this case the specifics of the experimental

manipulation may play a role in highlighting the predicted compared to the utilitarian value of the FB. All considered, it seems that the formulation "better or worse than expected" (Eppinger et al., 2008; Holroyd & Coles, 2002) adequately captures the core feature of the FB driving the corresponding FRN modulation, where "better" and "worse" can alternatively refer to monetary reward, accuracy of performance, or accuracy of action-outcome predictions. However, the actual sensitivity of the FRN to the interactive effect of valence (e.g., reward magnitude) with expectancy (e.g., reward likelihood) is still not completely ascertained, also due to large inconsistencies across existing studies regarding the FRN quantification. Some of the principal issues in the FRN quantification are whether a difference-wave between valence levels is computed, the assessment as average activity in a defined time-window compared to peak detection, and in the latter case whether the overlap with temporally contiguous positive deflections is controlled for. In this thesis, we sought to investigate this issue (see Chapter 2).

2.2.2.2. Signed or unsigned RPE signal?

Reaching a consensus about the factors determining the FRN amplitude modulation during PM is highly desired for either corroborating or disconfirming theoretical models that have been put forward to account for its neurophysiological mechanisms. Existing theoretical accounts of PM in the psychophysiology literature largely differ with regard to how information is processed to eventually generate an adaptation signal (e.g., need for control). These theories are often grounded in a predictive coding framework, according to which the occurrence of a prediction error signal (PE) triggers the need for control and adaptation, but they differ with regard to the nature of this error signal.

Probably the most influential model, the reinforcement learning theory (RL-ERN, Holroyd & Coles, 2002), assumes that the FRN (and likewise

the response-level ERN) reflects a signed PE (or reward prediction error – RPE), allowing PM to differentiate action outcomes as either better or worse than expected. This model bridged the electrophysiology of PM with the neurobiology of reinforcement learning (Schultz et al., 1997). More precisely, it originally posited that the sensitivity of ERN and FRN to error detection and incorrect FB is the result of a negative reinforcement learning signal, generated in dopaminergic neurons of the mesencephalic VTA (Schultz et al., 1997), and conveyed to the ACC where these two ERP components are eventually generated. These dopaminergic RL signals would train the ACC to act as a motor control filter, in service of performance optimization. Crucially, upon the receipt of a negative RPE signal (i.e., a phasic dip in DA activity), a phasic disinhibition of motor neurons in the ACC would generate the typical fronto-central negative deflection (FRN). In probabilistic learning tasks (e.g., Frank, Woroch, & Curran, 2005), this pattern of ACC activity is reflected as learning-related changes at the level of the ERN and FRN components: as the system learns the association between response and FB throughout the course of the task, RPE amplitude increases for incorrect responses (ERN) and decreases for incorrect FB (FRN). In other terms, the error-related negativity "propagates back in time" from the FB to the response (Holroyd, Pakzad-Vaezi, & Krigolson, 2008) as a function of the internalization of the action-outcome association (i.e., learning). The RL theory has received a few adjustments since its first formulation. In particular, a reinterpretation of the FRN has been proposed (Eppinger et al., 2008; Holroyd et al., 2008): the observed difference in FRN between negative and positive FB can be better explained by a positivity associated with better than expected outcomes, rather than a negativity associated with worse than expected ones (see also Proudfit, 2015). More specifically, as mentioned in the previous section, the error-related negative deflection characterizing the FRN for negative outcomes is likely equivalent to the stimulus-locked N2 (Baker & Holroyd, 2011; Towey, Rist, Hakerem, Ruchkin, & Sutton,

1980), and associated with task-relevant events in general (e.g., stimulus novelty or unexpected outcomes). Instead, a positive deflection is thought to be generated specifically in case of positive FB, thanks to a positive RPE (phasic increase in dopamine activity) that would inhibit or reduce the "default" N2. This positivity has been named feedback correct-related positivity (fCRP; Holroyd et al., 2008) or more recently, reward positivity (RewP; Proudfit, 2015). It is elicited in the time range of the N2, and signals a neural process linked to the achievement of the task goal (i.e., positive RPE). The open question, crucial for the tenets of the RL theory, is whether the N2 is suppressed for positive FB (particularly if unexpected) directly due to phasic DA inhibition on ACC (Hajihosseini & Holroyd, 2013; Holroyd, Krigolson, & Lee, 2011), or indirectly from the superposition of a positivity generated "elsewhere" in the brain (e.g., the following P3). Chapter 2 sought to address this question using an advanced topographical ERP mapping method, enabling to parse the contributions of different and overlapping components to the FRN/RewP.

According to alternative accounts and empirical evidence, the FRN reflects exclusively the salience of the FB, being compatible with a unsigned PE (i.e., absolute deviation from expectancy) (Ferdinand et al., 2012; Oliveira et al., 2007; Talmi et al., 2013). Compatible with this view, the predicted response-outcome (PRO) model (Alexander & Brown, 2011) proposed that the medial prefrontal cortex (mPFC – including the ACC) is concerned with learning to predict multiple possible action outcomes concurrently, and independently of their valence. The associated prediction signals would be inhibited when the predicted outcome occurs, resulting in maximal mPFC activity when an expected outcome fails to occur (thus, compatible with the FRN phenomenology). In this framework, the function of PE (reflecting surprise) from the mPFC is to train and update the predictions of response outcome. Moreover, this surprise signal may modulate learning rate of subsequent action-outcome association, and increment proactive and reactive control (Braver, 2012).

Hence, CC is conceived as the result of comparison between probable and actual action outcomes, but this comparison does not rely on the rewarding or aversive nature of the FB.

Finally, another influential model of CC, and developed somewhat independently from the predictive coding framework, proposed a link between PM, ACC activity, and error commission. The conflict monitoring hypotheses (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Botvinick, Cohen, & Carter, 2004) argued that the mechanism for detecting the need for augmented control pivots on monitoring and detecting conflicts during information processing (e.g., competition between responses). These authors proposed that errors are associated with conflict because of an interference between the pathways leading to correct and incorrect responses (see also Yeung, Botvinick, & Cohen, 2004). For instance, during and after error commission, the processing of the response-cueing stimulus may still be going on, generating the concurrent and conflicting representation of the alternative (correct) response. Interestingly, this model leveraged on empirical evidence indicating that conflict detection (e.g., response competition) is among the functions ascribed to the ACC (Carter et al., 1998). In this view, the strong association between response errors and ACC activity is simply due to the higher probability of incorrect responses when high response conflict is in place. This model unified in a single framework the link between ACC activity and the generation of a fronto-central negative deflection observed during incorrect responses (eliciting the ERN), as well as during response inhibition (eliciting the N2), where no overt response is produced (Yeung et al., 2004). On the other hand, it can hardly explain the similar negative deflection at the level of the FB (FRN), since the function of a hypothetical post-FB conflict signal is unclear (Walsh & Anderson, 2012). Nevertheless, a final note pertains to the possibility of unifying the conflict monitoring hypothesis of the ACC with the RL-ERN theory. More precisely, the RL-ERN theory leaves somehow unspecified the function of the ACC activity, beyond the assumption that it

is modulated by dopaminergic RPE. Assuming this function is primarily conflict related (as opposed to reflecting error detection or prediction violation), the phasic dopamine signals elicited by (unexpected) positive FB could train the ACC to execute behavior in a manner that minimizes response conflict (Holroyd, 2004; Holroyd et al., 2008).

In conclusion, two decades of extensive electrophysiological research did not tame the debate on the putative link between this ERP component (FRN or ERN) and DA-dependent RPE (Cohen, Wilmes, & van de Vijver, 2011; Ullsperger, Fischer, et al., 2014). Yet, there is abundant evidence showing that the FRN/RewP integrates outcome valence and expectancy (for reviews, see San Martín, 2012; Walsh and Anderson, 2012), as well as reflects intra and inter-individual sensitivity to reward (Proudfit, 2015; Weinberg & Shankman, 2017).

2.2.3. Frontal Midline Theta.

As mentioned in the previous sections, the ERP seen at the FB level (and somehow equivalent to the ERP time-locked to stimulus and to response) is characterized by a complex of positive-negative-positive deflections observable mostly at fronto-central channels (Ullsperger, Fischer, et al., 2014). The resulting waveform has a clear spectral representation in the theta band (4-8 Hz). As a consequence, time/frequency convolution of the EEG signal shows increased frontal midline theta power (FMT) for novel or surprising stimuli, conflict-related and incorrect responses (respectively pre- and post-response onset), and for negative compared to positive FB. This observation led some authors to hypothesize that this family of ERP components has a specific oscillatory signature (Luu & Tucker, 2001; Luu, Tucker, Derryberry, Reed, & Poulsen, 2003; Luu, Tucker, & Makeig, 2004). As a matter of fact, standard analytic methods (e.g., band filters) does not allow to discriminate whether scalp-level EEG activity reflects phase resetting of

ongoing oscillatory activity (i.e., phase synchronization upon event; Makeig, Debener, Onton, & Delorme, 2004), or phasic peaks reflecting temporally-discrete neural ensemble firing (Yeung, Bogacz, Holroyd, Nieuwenhuis, & Cohen, 2007). Focusing on changes in power of non-phase-locked EEG activity (i.e., induced power), as analyzed with time/frequency convolution methods (Cohen, 2014), may help to solve this problem. Regardless of this debate, conceptualizing EEG data as result of oscillatory neural activity – and analyzing band-specific power changes across time – can provide new and critical insight into mechanisms of PM, and more generally CC.

2.2.3.1. Novelty, conflict, error: surprise.

As mentioned above, the ERP complex observable during several stages of PM can also be conceived as a power increase in the theta-band, time locked to the eliciting event (e.g., cue stimulus, response, or FB), and lasting a few cycles. This power change after the event (with unit in µV2) is usually assessed with reference to the frequency-specific power in a pre-event time window, and the resulting ratio is converted to the logarithmic scale (resulting unit in dB). Accordingly, short bursts of FMT power are elicited during response errors in flanker tasks (Cavanagh, Cohen, & Allen, 2009), consistent with the activity of an action-monitoring system, and more specifically in line with a conflict detection account (Cohen & Cavanagh, 2011). More recent studies adopting task-switching paradigms identified FMT activity associated to both proactive and reactive control processes (Cooper et al., 2015), and the variance in trial-by-trial FMT power predicted the efficacy of cognitive control, reflected in reduced switch cost at the behavioral level (Cooper et al., 2019). The association of FMT power changes with a range of events eliciting novelty, conflict, error detection, and unexpected reward omission, suggests that this neurophysiological signal may primarily signal “surprise”. In an

influential review paper, Cavanagh and Frank (Cavanagh & Frank, 2014) proposed that this surprise signal reflects a functional property shared across all these eliciting events: realizing the need for augmented control over information processing. Moreover, FMT may provide a biologically plausible EEG correlate of the medial prefrontal cortex, whose function is to detect this need, and subsequently implement such control by entraining local and long-range brain networks (see also Cohen et al., 2011). Interestingly, conflict appears to preferentially modulate FMT signals that are non-phase-locked to the conflict-eliciting stimulus (Cohen & Donner, 2013), supporting the view that the modulation of ongoing FMT oscillations underpins CC.

2.2.3.2. Unsigned PE signal for control.

Learning-related changes in FMT oscillations have previously been reported in studies adopting probabilistic learning tasks, where the strength of the stimulus-response mapping is systematically manipulated by means of evaluative (i.e., performance-related) FB (Cavanagh, Figueroa, Cohen, & Frank, 2012; Cavanagh, Frank, Klein, & Allen, 2010a; Cohen, Elger, & Ranganath, 2007; Cohen et al., 2011; van de Vijver, Cohen, & Ridderinkhof, 2014). In these studies, increased power and phase coherence in FMT are regularly reported for errors compared to correct responses, and for negative compared to positive FB. Moreover, reward probability also modulates FMT activity, mirroring the amplitude changes of the ERN and FRN in analogous RL tasks (Eppinger et al., 2008). Among the existing studies, Van de Vijver (2014) convincingly showed that the activity peak of FMT on incorrect trials shifted from a post-feedback to a post-response time window as a function of learning: the larger the reward probability, the faster was the learning process and more anticipated (response vs FB) were the FMT power peaks. This correspondence of learning dynamics and FMT activity points toward a

role of this neurophysiological signal in signaling the violation of performance expectations that dynamically develops during RL. Yet, beside this primary modulation by expectancy, FMT power during a RL task is also usually stronger after negative compared to positive FB (Cavanagh, Frank, Klein, & Allen, 2010b; van de Vijver et al., 2014). At difference with the ERN and the FRN, FMT power usually does not show an interactive effect of FB outcome with reward expectancy, suggesting that this signal is likely representative of expectancy violation (Hajihosseini & Holroyd, 2013). This “asymmetrical” sensitivity to unsigned prediction errors is possibly related to behavioral adjustment strategies (Cavanagh et al., 2012), where errors entails a stronger heuristic value in guiding learning, as compared to correct responses. In sum, the pattern of FMT results shown during RL is thought to reflect the need for control instantiated by the ACC, irrespective of the sign of afferent RPE.

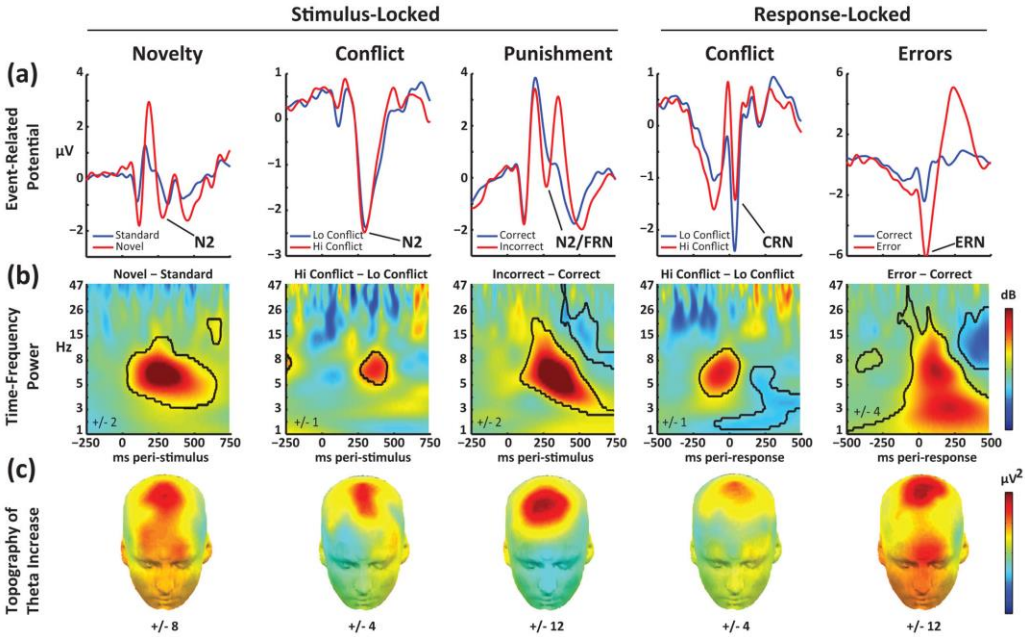

Figure 1. A variety of eliciting events is associated with a similar electrical signature on the scalp. (A) Traditional event-related potential (ERP) components in the time-domain. N2: an ERP component elicited by novelty or stimulus/response conflict. Feedback Related Negativity (FRN): A similar N2-like component elicited by external feedback signaling that one's actions were incorrect or yielded a loss. Correct-Related Negativity (CRN): a small, obligatory component evoked by motor responses even when these are correct according to the task, and enhanced by response conflict. Error Related Negativity (ERN): A massive ERP component evoked by motor commission errors. While these ERP components (i.e., peaks and troughs in the signal locked to particular external events and averaged across trials) are related to learning and adaptive control, they represent a small fraction of ongoing neural dynamics. (B) Time-frequency plots show richer spectral dynamics of event-related electrical activity which allow one to study power following particular events without requiring signals to be phased-locked. Here, significant increases in power to novelty, conflict, punishment and error are outlined in black, revealing a common theta-band feature. (C) Scalp topography of event-related theta activity. The distribution of theta power bursts is consistently maximal over the frontal midline (from Cavanagh & Frank, 2014).

2.3. Influence of effort anticipation and exertion on PM.

So far we briefly reviewed the mechanisms of PM and CC recruitment, with a focus on which type of information carried by evaluative FB (i.e., performance related) reliably modulates the FRN/RewP ERP component, as well as FMT oscillations. Among the factors that are expected to affect these EEG markers, relatively little attention has been given to the role of effort. This paucity is somewhat surprising given that theoretical models of PM are expected to account for the mechanism by which CC is recruited and allocated in service of goal attainment. Therefore, the difficulty of the task being executed, and the associated effort required, are both expected to be relevant task features to monitor during goal directed behavior.

Mental effort can be defined as what mediates between (a) the target task's characteristics and the subject's information-processing capacity and (b) the fidelity of the actual information-processing performance (Shenhav et al., 2017). In simpler terms, effort can be quantified as the difference between the actual and the maximal performance attainable. It should be noted, however, that empirical investigations often equate effort with task difficulty, under the assumption that increasing task demands would necessarily increase effort exertion as well (i.e., actual performance being constant). Tasks, and particularly cognitive operations, are perceived as effortful when they are time consuming and thus involve an opportunity cost (Kurzban, Duckworth, Kable, & Myers, 2013), when they are error-prone (Dunn, Inzlicht, & Risko, 2017), and more generally, when they require control-dependent over automatic processing. In fact, a variety of control-dependent processes, including inhibiting habits, working memory maintenance, task switching, and sustaining mental reasoning, are generally perceived as effortful. Shenhav and colleagues (2017) recently proposed that the instantiation of cognitive control, i.e. to "reconfigure information processing" away from default modalities, mediates cognitive effort.

Considering the literature on reward processing and value-based decision making, there are two opposing views about the role of effort: effort as cost, according to which effort is disutility and carries a negative value, and effort valuation, according to which effort can add value to a performance outcome, or even to an effortful option itself (Inzlicht, Shenhav, & Olivola, 2018). The first view explains phenomena like the effort discounting effect, such that the net value of reward is lower if it is hard to obtain (Botvinick, Huffstetler, & McGuire, 2009), and that effortful choices are preferably avoided (Apps et al., 2015; Chong et al., 2017). Interestingly, on the other hand, despite the fact that more demanding response requirements are less preferred compared to easier responses ("law of less work"; Hull, 1943), humans also prefer conditioned reinforcers that follow greater effort ("contrast effect"; Alessandri, Darcheville, Delevoye-Turrell, & Zentall, 2008): the value of a reinforcer is judged relative to the value of the event that preceded it (e.g., aversive effort exertion). Moreover, effort exertion can increase the sensitivity to following reward, as suggested by increased BOLD response of reward-related areas (subgenual ACC and striatum) when a rewarding outcome depends on a correct response compared to when it is randomly assigned (Zink, Pagnoni, Martin-Skurski, Chappelow, & Berns, 2005), or when reward follows mental effort (Hernandez Lallement et al., 2014). From an electrophysiological perspective, in line with this latter account, preliminary empirical evidence indicates that cognitive effort exertion may impact on the way we evaluate rewards. More specifically, increased RewP amplitude was elicited by a FB indicating correct performance following high compared to low difficulty arithmetic (Ma, Meng, Wang, & Shen, 2013; Wang, Zheng, & Meng, 2017). These results seem to indicate that effort investments change the subsequent hedonic impact of the performance's outcome, so that higher reward valuation comes with harder work deployed for its attainment. In sum, and as recently pointed out (Inzlicht et al., 2018), beside classical models in behavioral economics and

neuroscience stating the averseness of effort, growing evidence also supports the symmetrical view: effort can add value to its own products, and can itself be endowed with value.

An open question, especially from an electrophysiological perspective, regards how the anticipation of cognitive effort impacts on PM and task performance. More specifically, it is currently unclear which are the mechanisms whereby effort anticipation would lead to additional CC allocation and motivational invigoration, to eventually cope with the increased demands. When considering the early anticipatory phase, a line of research adopting fMRI identified a dopaminergic midbrain area (substantia nigra - SN) that shows enhanced activity for the anticipation of high attentional task demands (Boehler et al., 2011); moreover, a network of areas including midbrain, striatum, thalamus, and ACC exhibited an interaction between the anticipation of attentional demands and reward, suggesting that a neural mechanism for recruiting and allocating resources may be jointly modulated by the expected value and the cognitive demands of a task (Krebs, Boehler, Roberts, Song, & Woldorff, 2012). Similarly, the overlapping activation of striatum and dorsal ACC was also reported when anticipating an upcoming effortful task or monetary reward separately (Vassena et al., 2014). Interestingly, the effects of reward and task demand anticipation can be temporally dissociated when resorting to EEG (Schevernels, Krebs, Santens, Woldorff, & Boehler, 2014): cued reward availability can trigger task-preparation processes in an early phase, as reflected in early-onset negativity of the contingent negative variation (CNV) slow-wave component of the EEG. In turn, cued attentional demands affected only the late part of the CNV, likely reflecting top-down preparation for response.

In addition to the studies mentioned above, accumulating evidence indicates that the ACC activity tracks effort, and more specifically the cost of CC (Inzlicht, Bartholow, & Hirsh, 2015; McGuire & Botvinick, 2010; Sayalı & Badre, 2019). This growing empirical evidence helped updating

or formulating new computational models about the integrative mechanism by which the ACC monitors conflict during information processing (Botvinick et al., 2004), learns about action-outcome associations for action selection (Holroyd & Coles, 2002), and guides decision making (Rushworth, Walton, Kennerley, & Bannerman, 2004). Of outstanding interest, the Expected Value of Control (EVC) theory proposed that this range of ACC functions can be ultimately unified in the allocation of control based on its expected value, being reliant on expected payoff, amount of control needed, and cost of cognitive effort (Shenhav et al., 2013). Verguts and colleagues (Verguts, Vassena, & Silvetti, 2015) proposed a neurocomputational model of effort investment according to which effort exertion can be learned, relying on rewards, costs, and task difficulty. This model integrates the coding for both value and effort by the limbic loop (including ACC and striatum) in a single RL framework, where the output is a binary option on whether or not boosting effort exertion by reinforcing stimulus-outcome pathways (increasing signal-to-noise-ration in cortical areas). Sharing some similarities, the Hierarchical Reinforcement Learning model (Holroyd & Yeung, 2012) was built by reconsidering neurological evidence that apathy (akinetic mutism) is the most consistently reported consequence of ACC lesion, and thus pointing to the motivating role of ACC on effortful behavior. The model proposes that ACC learns, selects, and helps maintaining extended sequence of behavior in service of goal achievement. Hence, in comparison to the earlier RL-ACC theory, what is learned is the value of the task as a whole, in addition to the single action-outcome contingencies within the task.

Although a more detailed characterization of computational models of ACC is outside the scope of this work, these models help unifying the plethora of punctual empirical results in the field by building articulated and falsifiable theories of brain functions, including PM and CC allocation, with a pivotal role envisioned therein for this dorsal medial frontal area. Moreover, they allow to draw new and testable predictions on

physiological indexes of brain activity. Provisional attempts in this direction have already been made (Holroyd & Umemoto, 2016; Vassena, Deraeve, & Alexander, 2017). As outlined in the previous sections, FMT from the ACC seems to be tied with conflict detection and the need for control (Cavanagh & Frank, 2014), and cognitive effort exertion (Cooper et al., 2019; Mussel, Ulrich, Allen, Osinsky, & Hewig, 2016; Wascher et al., 2014). Relying on the HRL-ACC theory, Holroyd and Umemoto (2016) recently proposed that FMT could be viewed as an index of ACC's effortful control, in addition to the RewP component being a marker of reward valuation. Accordingly, in an extended and cognitively demanding time estimation task (Umemoto, Inzlicht, & Holroyd, 2018), they reported FMT power increasing with time-on-task, possibly reflecting increasing effort exertion to maintain stable performance.

More avenues remain open to exploration and, in this context, special effort should probably be devoted in testing model predictions about cognitive effort exertion as mediated by FMT, as well as the threshold above which effort anticipation leads to reward devaluation (effort discounting).

3. Outline Of The Dissertation

With the introduction above we presented a selected review of the literature at the crossroad between the affective neuroscience of hedonic processes and electrophysiology of performance monitoring. On the one hand, we showed how the integration of reward processing with effort exertion proved to be a fruitful operationalization of human motivation. On the other hand, we outlined the current understanding of the neural source, cognitive and affective significance, and computational nature of a set of EEG signatures of PM, with specific attention to the ones elicited by evaluative FB (i.e. FMT/RewP and FMT).

Consistent with this rationale, the overarching goal of this doctoral thesis is twofold. First, we sought to gain insight into the functional significance of these EEG markers of PM. To do so, we addressed unresolved methodological issues in the measurement of the FRN/RewP ERP component, being also critical for its theoretical implications; we sought to replicate and extended previous results regarding the modulation and functional significance of this ERP component, as well as FMT oscillations, when manipulating reward outcome and reward probability in a gambling task and in a probabilistic learning task; importantly, we also probed their modulation when integrating effort anticipation and reward processing in a novel experimental paradigm. Second and foremost, we concurrently leveraged on these EEG signatures of PM to try to unveil neural mechanism of reward processing and reinforcement learning, cognitive effort anticipation or exertion, and their integration in goal-directed motivated behavior. To do so, we resorted on both healthy student population, and on a sample of anhedonic, treatment resistant MDD patients.

In Chapter 2, we started with a detailed methodological investigation of the FRN ERP component elicited by evaluative FB during performance monitoring. We adopted a widely used gambling task and manipulated the

valence and expectancy of monetary FB. As reviewed in the previous sections, convergent evidence points to the functional role of this specific ERP component in signaling whether a given outcome is better or worse than expected, thus endowing this component with both an affective (reward processing) and cognitive (performance monitoring) relevance. Critically, a clear definition of the parameters determining the modulation of this signal is required to corroborate, or disconfirm, theoretical models proposed to account for its functional significance, as well as the underlying computational mechanism bearing on its main putative intracranial source (i.e. the ACC). We identified two core issues in the extant literature: I) the heterogeneity in the scoring methods adopted for this ERP component, and II) the failure of the conventional scoring methods in ascertaining whether the EEG deflections elicited by positive and negative FB reflect a unitary process, or rather dissociable neurocognitive processes arising from non-overlapping brain networks. We thus provided our contribution to the extant debate, by comparing the main scoring methods of the FRN available in the literature with an alternative topographic mapping analysis. With the latter approach we leveraged on the scalp distribution of the electric signal generated after FB onset, to provide an unbiased estimation of the influence of valence and expectancy to the temporal and topographic representation of the corresponding ERP waveform.

In Chapter 3, we devised and tested a novel experimental paradigm suited to explore the sensitivity of the FRN component and FMT oscillations to the integration of reward with cost anticipation. Besides addressing specific electrophysiological questions related to the functional role of these signals, such a paradigm aimed to tackle the second main objective of the thesis: leveraging on the electrophysiology of PM to investigate human motivation as a process highly reliant on the integration of reward with cost information. As reviewed in the previous section, the overarching function of the ACC that is thought to give rise to these EEG

signals appears to be signaling the need for adjustment to achieve behavioral goals (Ridderinkhof, Ullsperger, et al., 2004). Accordingly, the rationale of our study stemmed from the assumption that during PM, two main processes are proposed to converge in the medial frontal cortex (i.e., ACC, or RCZ), the likely source of both the FRN/RewP and FMT oscillations. The first is reward processing, and more precisely DA-dependent reward prediction errors (Holroyd & Umemoto, 2016; Proudfit, 2015). The second (and related) process is realizing the need for augmented control over information processing, and the implementation of such control, possibly by means of FMT mediated entrainment of areas directly involved in CC, such as the dlPFC (Cavanagh & Frank, 2014). We reasoned that, similarly to the wide range of phenomena triggering the need for control (see section 2.2), the disclosure of effort information at the FB level (to be subsequently exerted) should also influence the need for additional control on task performance (FMT power), and possibly the reward value of the FB (FRN/RewP amplitude). Hence, this study allowed us to test some theory-based predictions about these signals. Moreover, this was our first attempt to assess the utility of these EEG signals for studying the fundamental processes of reward and effort integration underpinning motivation.

In Chapter 4, we followed up on the previous experimental design, but this time we focused on integration between reward processing and cognitive effort. As discussed in section 2.3, cognitive effort possesses a double role in cost-benefit decision making, as humans tend to avoid it, but also to valuate more rewards attained with it (Inzlicht et al., 2018). First, we adapted the previous experimental paradigm to combine a gambling task with an orthogonal cognitive effort task (arithmetic calculation). Second, with this new experimental design we addressed a number of methodological issues inherent to the previous study, including contrasting two conditions that only differed regarding their level of cognitive effort. We ran first a behavioral experiment and focused on subjective ratings of FB,

where we replicated a core finding of Chapter 3, translating increased reward valuation for effort avoidance. In a second experiment where we used 64-channel EEG, our primary goal was to verify whether FRN/RewP amplitude changes at the FB level could reflect I) increased reward for cognitive effort avoidance, and II) increased reward after effort exertion.

In Chapter 5, we adopted a rather different approach to investigate the likely and complex intersection between motivation, reward processing, and PM. First, we studied PM from a reinforcement learning perspective (Eppinger et al., 2008; Frank et al., 2005), instead of a gambling task (Chapters 2-4). Second, this time we leveraged on EEG to assess possible motivational impairments in a sample of severely anhedonic, treatment resistant unipolar depressed patients, compared to healthy controls. We adopted a probabilistic learning task, in which the manipulation of reward probability and FB outcome were critical to create variable stimulus-response associations. Notably, in this context, PM is a highly dynamic and time-evolving process, whereby evaluating the accuracy of the response, initially reliant mostly on the evaluative FB, gradually shifts to the response level as a function of learning. In fact, through learning, the agent can somehow “internalize” (i.e. form and use a mental representation) these stimulus-response associations. Moreover, different levels of stimulus-response associations translated varying effort requirements for the different conditions embedded in this experimental design. We compared the behavioral performance and FMT power oscillations between healthy controls and a large cohort of MDD patients. Capitalizing on the functional role of FMT oscillations evidenced in the previous studies, we titrated changes of this specific neural signal at both the response and FB levels occurring as a function of time. Consistent with theoretical models assuming FMT as a valid marker of need for control (Cavanagh & Frank, 2014) and/or effortful control (Holroyd & Umemoto, 2016), we expected blunted FMT power at the FB level in MDD patients

compared to matched healthy controls, specifically when reinforcement learning was hard because reward probability was low.

As last part of this thesis, a general discussion of the main findings gathered in these four empirical chapters is proposed. There, we seek to discuss the main methodological and theoretical implications resulting from these different studies. We argue why and how we believe harnessing the electrophysiology of performance monitoring can turn out to be especially informative to shed light on the neural mechanism of reward and motivation, as well as their complex interplay, in humans.

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Chapter 2: Dissociable effects of reward and expectancy during evaluative feedback processing[1]

[1] Gheza, D., Paul, K., & Pourtois, G. (2018). Dissociable effects of reward and expectancy during evaluative feedback processing revealed by topographic ERP mapping analysis. International Journal of Psychophysiology, 132, 213–225.

1. Abstract

Evaluative feedback provided during performance monitoring (PM) elicits either a positive or negative deflection ~250-300 ms after its onset in the event-related potential (ERP) depending on whether the outcome is reward-related or not, as well as expected or not. However, it remains currently unclear whether these two deflections reflect a unitary process, or rather dissociable effects arising from non-overlapping brain networks. To address this question, we recorded 64-channel EEG in healthy adult participants performing a standard gambling task where valence and expectancy were manipulated in a factorial design. We analyzed the feedback-locked ERP data using a conventional ERP analysis, as well as an advanced topographic ERP mapping analysis supplemented with distributed source localization. Results reveal two main topographies showing opposing valence effects, and being differently modulated by expectancy. The first one was short-lived and sensitive to no-reward irrespective of expectancy. Source-estimation associated with this topographic map comprised mainly regions of the dorsal anterior cingulate cortex. The second one was primarily driven by reward, had a prolonged time-course and was monotonically influenced by expectancy. Moreover, this reward-related topographical map was best accounted for by intracranial generators estimated in the posterior cingulate cortex. These new findings suggest the existence of dissociable brain systems depending on feedback valence and expectancy. More generally, they inform about the added value of using topographic ERP mapping methods, besides conventional ERP measurements, to characterize qualitative changes occurring in the spatio-temporal dynamic of reward processing during PM.

2. Introduction

Performance monitoring (PM) is crucial to foster goal adaptive behavior. According to most recent models (Ullsperger et al., 2014a) it is best conceived as a feedback loop whereby action values are learned and updated, especially when mismatches between goals and actions occur unexpectedly. Although these mismatches can sometimes be processed based on internal or motor cues (e.g., response errors), in many situations, external evaluative feedback provides the primary source of information to guide the course of PM. At the psychophysiological level, there has been a rich tradition of event-related brain potentials (ERP) research aimed at exploring the putative brain mechanisms underlying this loop during feedback-based PM.

Traditionally, the feedback-related negativity (FRN, sometimes termed FN, fERN, or MFN) was put forward as the main electrophysiological correlate of evaluative feedback processing during PM (Holroyd and Coles, 2002; Miltner et al., 1997; Ullsperger et al., 2014b; Walsh and Anderson, 2012). The FRN corresponds to a phasic negative fronto-central ERP component (N200) peaking around 250 ms after evaluative feedback (FB) onset, being typically larger for negative compared to positive outcome, as well as unexpected relative to expected one. This negative deflection is usually preceded by a positive ERP component (P200; Sallet et al., 2013), as well as followed by the P300, corresponding to a large positive deflection being maximal around 300-400 ms at central and posterior parietal scalp electrodes.

Initially, amplitude changes of the FRN (very much like the ERN, error-related negativity, which is time-locked to response onset) have been interpreted against a dominant reinforcement learning theory (RL-ERN theory; Holroyd and Coles, 2002; Sambrook and Goslin, 2015; Walsh and Anderson, 2012). In this framework, changes in the amplitude of the FRN capture indirectly dopaminergic-dependent reward prediction error signals

(RPE; i.e. outcome either better or worse than expected). Moreover, the (dorsal) anterior cingulate cortex (dACC, sometimes termed rostral cingulate zone - RCZ; Ullsperger et al., 2014a) is thought to be the main intracranial generator of this phasic ERP component (Gehring and Willoughby, 2002; Miltner et al., 1997; Yeung et al., 2004; Yu et al., 2011). According to the RL theory, the FRN reflects the processing of the outcome along a good-bad (valence/outcome) dimension, in relation to its actual expectancy. In other words, the FRN is thought to provide an integrated neural signal during PM where both the salience (absolute prediction error) and the valence (signed prediction error) of the outcome are integrated (Holroyd and Coles, 2002; Ullsperger et al., 2014). Consistent with this view, many ERP studies previously reported reliable changes of the FRN amplitude as a function of not only the valence of the feedback, but also its expectancy, usually manipulated by means of changes in reward probability across trials (for reviews, see San Martín, 2012; Walsh and Anderson, 2012).

More recently, researchers have begun to explore reward processing per se, as opposed to RPE. As a matter of fact, when the emphasis is put on reward processing at the feedback level (especially when monetary reward is used as main incentive), the amplitude difference seen at the FRN level (i.e. when reward is delivered vs. omitted) can be best explained by the generation of a positive activity associated with better than expected outcomes, rather than a negativity associated with worse than expected ones. In the existing ERP literature, this positivity has been named the “feedback correct-related positivity” (fCRP; Holroyd et al., 2008) or the “reward positivity” (RewP; Proudfit, 2015). It is elicited in the time range of the N200, and is thought to signal the achievement of the task goal (i.e. obtaining a reward) (Foti et al., 2011; Holroyd et al., 2008; Proudfit, 2015). In keeping with the RL-FRN theory, Holroyd et al. (2008)

reinterpreted the N200 (Towey et al., 1980) giving rise to the FRN[2] as the neural signal indicating that the task goal has not been achieved. The N200 is usually elicited by task-relevant events in general (i.e. unexpected outcome regardless of its outcome, see also Ferdinand et al., 2012) and might thus be overshadowed by the concurrent positive deflection that is elicited by positive FB. Accordingly, given that the positive (RewP) and negative (FRN) deflections overlap in time, it remains nowadays partly unclear which of them best captures systematic changes in reward processing at the feedback level as a function of reward expectancy (San Martín, 2012). Comparing ERP amplitudes at certain or pre-defined sites elicited by positive (reward) or negative (no-reward) FB implicitly assumes a similar source of the EEG signal accounting for them. As a matter of fact, the question remains whether the N200 component giving rise to the FRN is actually reduced for positive FB due to direct inhibition of the RCZ for example (Hajihosseini and Holroyd, 2013; Holroyd et al., 2011, 2008), or alternatively, from the superposition of another (non-overlapping) component, being reward-related primarily and best expressed by the RewP. In agreement with this latter interpretation, Foti et al. (2011) provided evidence that such a positive component could result from the activation of the putamen within the basal ganglia (but see the methodological objections raised by Cohen et al., 2011; and the following reformulation in Proudfit, 2015). Further, the same authors (Foti et al., 2015) recently argued that the FRN may be a blend of loss- and gain-related neural activities, possibly reflecting the contribution of partly distinct networks. At variance with this interpretation, other authors contend that the dACC provides the main (and most plausible) source of both ERP components, and is actually the only cortical brain region whose

[2] Here we refer to “FRN” as the negative deflection elicited by no-reward FB, and to “RewP” as the positive deflection (or lack of negative one) elicited by reward FB. For ease of reading, in Methods and Results sections we will refer solely to the scoring method adopted for quantifying both deflections.

activation pattern is consistent with the observed modulation of their amplitude at the scalp level by valence and expectancy concurrently (Martin et al., 2009). Thus, a consensus about the neural generators of this FB-based ERP signal is currently lacking, and other potential sources have been put forward as well (among others, the ventral rostral anterior and posterior cingulate cortex; Luu et al., 2003; Nieuwenhuis et al., 2005).

Whereas the standard approach in ERP research consists of measuring the amplitude (and/or latency) of either the FRN or RewP at a few electrode positions, it usually falls short of confirming or disconfirming one of these competing assumptions, nonetheless. Using a standard ERP approach, it remains indeed impossible to confirm directly whether systematic changes in the amplitude of the FRN component occurs following local changes within the dACC with outcome valence and reward expectancy, or alternatively, another reward-related and non-overlapping component blurs this effect. To address this question, the standard ERP analysis can be supplemented by an advanced topographic ERP mapping analysis informing about the actual expression of the scalp configuration in the time range of the FRN and RewP (Murray et al., 2008; Pourtois et al., 2008). Furthermore, possible neural generators giving rise to them can be estimated with appropriate source localization methods. However, caution is needed when interpreting EEG source estimations. Converging evidence obtained when crossing different imaging techniques (such as EEG and fMRI for example) could eventually help validate and confirm localization results based on EEG only, as performed here.

Following standard practice (Keil et al., 2014), an ERP component is usually defined not only by its polarity, amplitude and latency, but also by its actual topography and neural generators. Topography refers here to the actual spatial configuration of the electric field at the time where the ERP component of interest, here FRN and RewP, is best expressed at the scalp level, including all channels available concurrently. Noteworthy, changes in the topography necessarily denote changes in the underlying

configuration of brain generators (Lehmann and Skrandies, 1980; Vaughan, 1982). Accordingly, characterizing ERP components accurately using complementing topographical evidence provides an important source of information regarding the actual (dis)similarity between conditions in terms of underlying brain networks; a level of analysis that cannot be reached directly when considering only the amplitude changes occurring at a limited number of electrode positions (usually Fz or FCz only in the case of the FRN). Further, some of these local amplitude changes can in principle be confounded or inflated by more global changes in the topography (and/or global strength) of the electric field across conditions, challenging the validity of some of the interpretations made when using a standard ERP analysis only. Moreover, local amplitude measurements at a few electrode positions strongly depend on the specific reference montage used. By comparison, the actual topography of an ERP component is reference-free (Murray et al., 2008). Additionally, a clear asset of recent topographical ERP mapping analyses (Michel and Murray, 2012) is that user/experimenter-related biases and priors can be strongly limited, including the selection of specific time-frames for further statistical analyses. In this framework, the main topographical components are revealed using a stringent clustering method that allows to identify the specific time periods in the ERP signal where they are best expressed. As a result, there is no need to select a priori specific electrode locations or time-frames for statistical analyses, decreasing ultimately the likelihood of type I error (Luck and Gaspelin, 2017).

Surprisingly, to the best of our knowledge, the topography of the FRN and RewP components have not been scrutinized yet in the existing ERP literature. For example, it remains currently unclear whether the FRN and RewP share common topographical variance, or instead, can clearly be dissociated from one another when considering this global level of analysis, especially when a high density montage (64 channels or more) is used. Further, possible modulatory effects of reward expectancy on the

topography of the FRN and RewP remain also poorly understood. However, such an analysis has the potential to address one of the main theoretical questions raised in the current ERP literature about these two ERP components and as reviewed above: is the negative component (N200) giving rise to the FRN clearly different (at the topographical level) relative to the RewP? Moreover, considering the topography as level of analysis can also shed new light on the actual interplay of feedback outcome with feedback expectancy. These questions lie at the basis of the current study.

To address them and inform about reward processing during externally-driven PM, we recorded high-density (64 channels) EEG in 44 adult healthy participants while they performed a previously validated gambling task (Hajcak et al., 2005) where FB outcome (reward vs. no-reward) and expectancy (low, intermediate of high reward probability) were manipulated on a trial by trial basis using a factorial design. First, we carried out a standard ERP analysis and extracted the mean amplitude of the FRN and RewP, using and contrasting different scoring methods available in the literature: peak to peak vs. mean amplitude measurement. Second and crucially, we ran an advanced topographic ERP mapping analysis on the exact same average ERP data time-locked to FB onset, and isolated the dominant topographical components accounting for them, in an unbiased way. For the standard ERP analysis, we surmised a larger FRN for no-reward compared to reward FB, with the opposite effect found for the RewP, as well as a possible modulation of each of these two ERP components by expectancy (i.e., larger amplitude for unexpected than expected outcome each time; Walsh and Anderson, 2012). At the topographical level, we tested the prediction that the FRN and RewP could lead to partly dissociable spatial configurations of the global electric field (i.e., topography), and hence non-overlapping intracranial generators, as has been suggested before. More specifically, given that the FRN is usually maximal at fronto-central scalp locations (for negative/no-reward

FB) and was previously related to the dACC (among others, Gehring and Willoughby, 2002; Miltner et al., 1997; Yeung et al., 2004; Yu et al., 2011), we conjectured that topographical ERP variance associated with no-reward could be associated with this specific brain region in our study. In comparison, since positive/reward-related ERP activity during FB processing was previously linked to activation in more posterior parts of the cingulate cortex (Cohen et al., 2011; Fouragnan et al., 2015; Nieuwenhuis et al., 2005), and/or specific regions of the basal ganglia (Foti et al., 2015, 2011), we hypothesized that these regions (especially the posterior cingulate cortex) could account for the reward-related activity during feedback processing in our study. Furthermore, we sought to explore whether these two spatial configurations of the electric field depending on FB outcome, if clearly dissociable from one another, could show a similar or instead different sensitivity to FB expectancy.

3. Methods

3.1. Participants.

Existing EEG data from two previous (and separate) studies by Paul and Pourtois (2017 - Experiment 1) and Gheza et al. (submitted – Experiment 2), where the same gambling task was used, were pooled together. A total of forty-five undergraduate students from Ghent University (right-handed, with normal or corrected-to-normal vision, and no history of neurological or psychiatric disorders) were included in the present study. They all gave written informed consent prior to the start of the experiment and were compensated about 30€ for their participation. The study by Paul and Pourtois (2017) had a between-groups design and involved a mood-induction paradigm. Only the control group (with a neutral-mood state, 25 participants) from this study and the whole sample (20 participants) from Gheza et al. (submitted, where no specific mood induction was used) were merged together. One participant had to be excluded due to noisy EEG recording. Hence, the total sample included 44 participants (34 females, age: M = 22.0 years, SD = 2.6). Both studies were approved by the local ethics committee at Ghent University. A post hoc power analysis was conducted using GPower (Faul et al., 2007). The sample size of 44 was used for the statistical power analyses and the power to detect a small (η^2=0.01), medium (η^2=0.06) or large (η^2=0.14) effect for the interaction between valence and expectancy was estimated. The alpha level used for this analysis was set to .05. The post hoc analyses revealed the statistical power for this study was .22 for detecting a small effect, .91 for detecting a medium effect size, and exceeded .99 for a large effect. Thus, this sample size was more than adequate to detect a moderate/large effect, but not a small one.

3.2. Stimuli and task.

A previously validated gambling task (Hajcak et al., 2007) was adapted and administered in both studies. On each and every trial, participants had to choose one out of four doors by pressing with their right index finger the corresponding key on the response box. After a fixation dot (700 ms) this choice was followed by either positive FB (green "+"), indicating a win, or no-reward FB (red "o") (1000 ms). The two studies differed slightly in the amount of monetary reward, being either 8 cents (Paul and Pourtois, 2017) or 5 cents (Gheza et al., submitted). At the beginning of each trial, participants were informed about reward probability with a visual cue (600 ms), followed by a fixation dot (1500 ms). This cue was presented in the form of a small pie chart shown at fixation. Either one, two or three quarters were filled (black/white) corresponding to a reward probability of 25, 50 or 75 %. A reward probability of 25% indicated that only one door contained the reward, two doors in the case of 50% reward probability and three doors for 75% reward probability. Unbeknown to participants, the outcome was actually only related to these objective probabilities (but not the actual choices made by them), ending up with a preset winning of €14.72 (Paul and Pourtois, 2017) or €12.40 (Gheza et al., submitted). Inter trial interval was fixed and set to 1000 ms. Hence, by crossing the three possible reward probabilities with the two opposite outcomes, six trial types were included in a factorial design[3]. To ensure participants paid attention to the cue and outcome, catch trials were randomly interspersed in the trial series. In 24 trials, at the cue offset they were asked to report their winning chance ("how many doors contain a prize?", allowing responses from 1 to 3). In 24 different trials, they were asked about the expectedness of the outcome at FB offset, and answers

[3] Beside the conditions described above ("regular" trials), the task for Gheza et al. (in preparation) also included "special" trials, that were discarded from the analyses conducted in the present study.

were collected by means of a visual analog scale (VAS) anchored with “very unexpected” and “very expected”.

All stimuli were shown against a grey homogenous background on a 21-in CRT screen and controlled using E-Prime (V 2.0, Psychology Software Tools Inc., Sharpsburg, PA).

3.3. Procedure.

In both studies, after reading the instructions, participants were first familiarized with the gambling task using 12 practice trials. The presentation of the 6 trial types (3 reward probabilities x 2 outcomes) was randomized, and the same trial type could be presented consecutively. The main experiment consisted of four blocks each comprising 92 (Exp. 1 – Paul and Pourtois, 2017) or 124 trials (Exp. 2 – Gheza et al., submitted). After each block, a short break was included and participants were informed about their current (cumulative) payoff.

In Paul and Pourtois (2017), a total of 368 trials was presented (80 with 50%, 144 with 25% and 144 with 75% reward probability). A neutral-mood induction procedure was applied before the task and repeated after each block to maintain the specific mood state (here neutral) throughout. In Gheza et al. (submitted), a total of 392 trials was used (104 with 50%, 144 with 25% and 144 with 75% reward probability).

3.4. Recording and Preprocessing of Electrophysiological Data.

EEG was recorded using a 64-channel Biosemi Active Two system (http://www.biosemi.com) with four additional electrodes measuring horizontal and vertical eye movements. EEG was sampled at 512 Hz and referenced to the Common Mode Sense (CMS) active electrode and

Driven Right Leg (DRL) passive electrode. The EEG was preprocessed offline with EEGLAB 13.5.4b (Delorme and Makeig, 2004), implemented in Matlab R2012b. A 0.05/35 Hz high/low pass filter was applied after re-referencing the EEG signal to the averaged mastoids. An independent component analysis was run on the continuous data to correct manually for eye artifacts and spatial or temporal discontinuities. Individual epochs were extracted from -250 to 750 ms around the FB onset and a pre-feedback baseline was subtracted (-250 to 0). A semi-automatic artefact correction procedure was applied to eliminate trials with voltage values exceeding ± 90 μV or slow voltage drifts with a stronger slope than ± 90 μV, as well as based on visual inspection. For each subject separately, artefact-free epochs were grouped according to the six main experimental conditions: expected, no-expectations[4] and unexpected FB associated with reward (deriving from 75%, 50%, 25% reward probability trials respectively), or expected, no-expectations and unexpected FB associated with no-reward (deriving from 25%, 50%, 75% reward probability trials respectively). To avoid different signal to noise ratios between conditions, the same number of trials (randomly sampled) was used for all of them, being defined subject-wise based on the condition with the lowest trial count.

3.5. Standard peak analysis.

FRN: peak to peak. The FRN and RewP were determined peak-to-peak at FCz (FRN-pp) as the difference between the most negative peak (N200: within 200 - 350 ms) and the preceding positive peak (P200: within

[4] The no-expectation term refers here to the objective reward probability and not the subjective expectation or uncertainty. The condition provides equal (objective) probability of reward or no-reward FB and therefore goes along with the highest uncertainty regarding feedback outcome during the experiment.

150 - 250 ms) assumed as the onset of the (relative) negativity (Holroyd et al., 2008, 2003).

FRN: mean amplitude. We also used an alternative scoring method for the FRN and RewP (FRN-m), defined at FCz as the mean amplitude within the 213-263 ms interval post-feedback onset (i.e. the 50 ms window surrounding the peak of the N200 for no-reward; Novak and Foti, 2015; see also Weinberg and Shankman, 2017 for the use of a mean-amplitude approach in a different time window). This time window and location were based on the FRN-pp maximal amplitude from the grand average of no-reward FB trials (merging all three expectancy levels; "collapsed localizer" approach, see Luck & Gaspelin, 2016).

P2 and N2. Supplementary peak analyses on P200 and N200 components (when considered separately) were carried out in order to verify their relative sensitivity to FB expectancy and its interaction with FB valence. In accordance with the FRN-pp scoring method, P200 was defined as the maximum positivity occurring within the 150-250 ms interval post FB onset, while the N200 as the maximum negativity within the 200-350 ms interval post FB onset.

3.6. Topographical ERP mapping analysis (TA).

The dominant topographies accounting for the ERP data set under scrutiny were extracted using CARTOOL software (Version 3.60; developed by D. Brunet, Functional Brain Mapping Laboratory, Geneva, Switzerland). The basic principles of this method have been described extensively elsewhere (Brunet et al., 2011; Michel et al., 1999; Murray et al., 2008; Pourtois et al., 2008). In short, it is based on two successive data analysis steps. First, the dominant topographical maps are isolated from the grand average ERP data by means of a clustering algorithm that takes into account the global dissimilarity, i.e. the difference in terms of

spatial configuration between two normalized maps independent of the global strength of the ERP signal (Lehmann and Skrandies, 1980). Next, these main and dissociable topographical configurations are fitted back to the individual subject ERP data and a quantification of their representation across subjects and conditions is then provided, including the global explained variance (or goodness of fit), the correlation and the time point of the best fit. Parametric tests are eventually performed on these variables in order to compare different experimental conditions at the statistical level.

TA: Segmentation. First, using a competitive T-AAHC cluster analysis (Topographic - Atomize and Agglomerate Hierarchical Clustering) (Brunet et al., 2011; Tibshirani and Walther, 2005) of the entire epoch (i.e. from -250 prior to and up to 750 ms following feedback onset, corresponding to 512 time frames-TFs at a 512-Hz sampling rate), the dominant topographical maps were identified. The specific (and default) settings for the clustering method followed the recommendations implemented in CARTOOL and were the following. 1) Minimum and maximum number of clusters were predefined to one and nine, 2) a smoothing kernel (Besag factor 10), of three TFs was applied, and 3) segments shorter than three TFs were rejected. The choice of the best segmentation result was based on an objective meta criterion of 7 criteria proposed previously (see Charrad et al., 2014) and visual inspection of the results.

TA: Fitting. The dominant topographies identified in the preceding step were then fitted back to the individual averages (n=6 per subject) to determine their expressions across participants and conditions. As the focus of the analysis was on reward processing (and expectancy), we mostly examined possible changes in the topography of the ERP signal as a function of reward and/or expectancy occurring 200-500 ms post-feedback onset, in keeping with many previous ERP studies (Foti et al., 2015; Hajcak et al., 2007; Sambrook and Goslin, 2015; Ullsperger et al., 2014b). Fitting parameters also followed the recommendations

implemented in CARTOOL and included 1) a smoothing kernel (Besag factor 10) of three TFs and 2) rejection of segments shorter than three consecutive TFs. The fitting procedure was done as a non-competitive process to validate that one of the topographic configurations fitted better than the other one depending on the condition (based on global explained variance - GEV - and the mean correlation of the map with the signal). Furthermore, the time course of these topographic maps could be evaluated, i.e. the TF of the best correlation could be compared between the maps and across conditions. If the last approach revealed a significant temporal difference between the dominant maps, the fitting procedure was repeated separately for the different time windows.

3.7. Source Localization.

To estimate the configuration of the neural generators underlying the previously identified reward related topographical maps, a distributed linear inverse solution was used—namely, standardized low-resolution brain electromagnetic tomography (sLORETA; Pascual-Marqui, 2002). sLORETA solutions are computed within a three-shell spherical head model coregistered to the MNI152 template (Mazziotta et al., 2001). LORETA estimates the 3-D intracerebral current density distribution within a 5-mm resolution. The 3-D solution space is restricted to the cortical gray matter and hippocampus. The head model uses the electric potential field computed with a boundary element method applied to the MNI152 template (Fuchs et al., 2002). Scalp electrode coordinates on the MNI brain are derived from the international 5% system (Jurcak et al., 2007). The calculation was based on the conditions specific average per subject in the time window of interest identified in the previous analysis.

3.8. Statistical Analysis.

At the behavioral level, the subjective ratings related to catch trials after the FB (probing FB expectation) were first transformed to percentages, arbitrarily setting one anchor ('very unexpected') to 0 and the other one ('very expected') to 100. These evaluations were considered to be correct if they fell within a ± 25% range around the correct response (see Paul and Pourtois, 2017 for a similar procedure). The amount of correct responses to these catch trials as well as catch trials corresponding to the cue (probing reward probability) were eventually reported as percentage of correct responses.

At the ERP level, repeated measures ANOVAs with FB expectancy (expected, no-expectations, unexpected) and outcome (reward vs. no-reward) as within-subject factors were performed (individual trial count, balanced across the six conditions: M = 27.4, SD = 4.3) separately for FRN-pp and FRN-m.

At the topographical level, each of the three dependent variables gained by the fitting procedure (i.e., GEV, mean correlation, TF of best correlation) was entered in a 2 x 3 x 2 repeated measurement ANOVA with the within-subject factors map configuration (FRN vs. RewP-map), expectancy (unexpected, no-expectations, expected) and FB valence (reward vs. no-reward). If the previous analysis based on TF of best correlation hinted at a potentially interesting difference in the time-course of the main maps, another ANOVA was run with the same within-subject factors, but adding a factor "time-window"(early vs. late).

The inverse-solution results were compared between the two reward outcomes (reward vs. no-reward) using paired-sample t-tests performed on the log-transformed data. To reveal potential differences in the inverse-solution space through direct statistical comparison, a stringent nonparametric randomization test was used (relying on 5,000 iterations, see Nichols and Holmes, 2001).

For all analyses, significance alpha cutoff was 0.05.

4. Results

4.1. Behavioral Results.

The accuracy for the cue (Mcorrect= 88.1 %, SD = 8.0) and for the outcome evaluation (Mcorrect = 60.7 %, SD = 25.3), as inferred from the catch trials, were high and well above chance level, suggesting that participants correctly monitored reward probability (based on the visual cue) and outcome (based on the feedback).

4.2. ERP Results.

FRN: peak to peak. The analysis performed on the FRN-pp amplitudes showed a significant main effect of FB valence ($F(1, 43) = 16.78$, $p < .001$, $\eta^2 = .281$) and an interaction between FB valence and FB expectancy ($F(2, 86) = 12.49$, $p < .001$, $\eta^2 = .225$). The FRN component was larger (more negative) for no-reward compared to reward FB (Mreward = -5.08, SE = 0.30, Mno-reward = -6.55, SE = 0.36). The multivariate simple effect of FB expectancy was significant for no-reward ($F(2, 42) = 7.06$, $p = .002$, $\eta^2 = .252$), but not for reward FB ($F(2, 42) = 1.65$, $p = .203$, $\eta^2 = .073$), confirming its sensitivity to RPE, when scored peak to peak[5] (see Fig. 1).

[5] In order to rule out that these neurophysiological effects were different between the two samples, we used a Bayesian factor analysis which is suited for estimating the amount of evidence in favor or against the null hypothesis (Rouder et al., 2017). More specifically, the data from the FRN-pp method was examined in a Bayesian repeated measure ANOVA in which the factors were FB outcome (reward or no-reward), FB expectancy (expected, no-expectations, or unexpected) and Group (Exp 1 or Exp 2). We used the JASP software package (JASP Team, 2017 - version 0.8.1.2) with default prior settings. First, the likelihood for each alternative models (derived from the combination of the 3 factors) was tested against a Null model. The models that best explained the variance were the main effect of Outcome, followed by the one including the two main effect of Expectancy and Outcome and their interaction (BF10 for Outcome = 40266, BF10 for Expectancy + Outcome + Expectancy * Outcome = 9031). In order to rule out the Group factor effects,

FRN: mean amplitude. The analysis performed on the FRN-m amplitudes showed a significant main effect of FB valence only ($F(1, 43) = 62.39$, $p < .001$, $\eta^2 = .592$), without a significant interaction between FB valence and FB expectancy, however ($F(2, 86) = 2.19$, $p = .118$, $\eta^2 = .048$). The FRN-m was larger (more negative) for no-reward compared to reward FB ($M_{reward} = 2.42$, $SE = 0.51$, $M_{no\text{-}reward} = -0.41$, $SE = 0.44$). These results indicated that, on this critical time window and fronto-central channel, the FRN, when scored using a stringent mean amplitude measurement, was sensitive to FB valence only (reward being present or absent), without any significant modulation due to FB expectancy (see Figure 1). Hence, these results suggest a qualitatively different outcome at the FRN level depending on the specific scoring method used.

P2 and N2. Repeated measure ANOVAs were run on the two components separately, with FB valence and FB expectancy used as within subject factors. The analysis for the P200 revealed significant main effects of Valence ($F(1, 43) = 9.23$, $p = .004$, $\eta^2 = .177$) and Expectancy ($F(2, 86) = 4.49$, $p = .014$, $\eta^2 = .095$). The analysis on the N200 revealed a significant main effect of Valence ($F(1, 43) = 47.64$, $p < .001$, $\eta^2 = .526$) and crucially, a significant interaction between Valence and Expectancy ($F(2, 86) = 6.45$, $p = .002$, $\eta^2 = .130$). Thus, although the FRN-pp scoring method could potentially inflate the effect of Expectancy driven by the P200 (as opposed to N200) component, it is clear from the N200 only

we then included the model terms Expectancy, Outcome and Expectancy * Outcome (i.e. flagged as Nuisance) in every model (including the Null model) and we looked at the BF01 (likelihood of the Null model over the others). The Null model (assumed probability of 1) was 6.8 times more likely to be true compared to the model including the main effect of Group (BF10 = 0.145), and much more likely compared to any other model that included an interaction with Group (BF10 < 0.068). These results provide moderate to very strong evidence for the absence of a Group effect on these FRN-pp results.

analysis that this deflection alone was significantly modulated by both factors concurrently in our study.

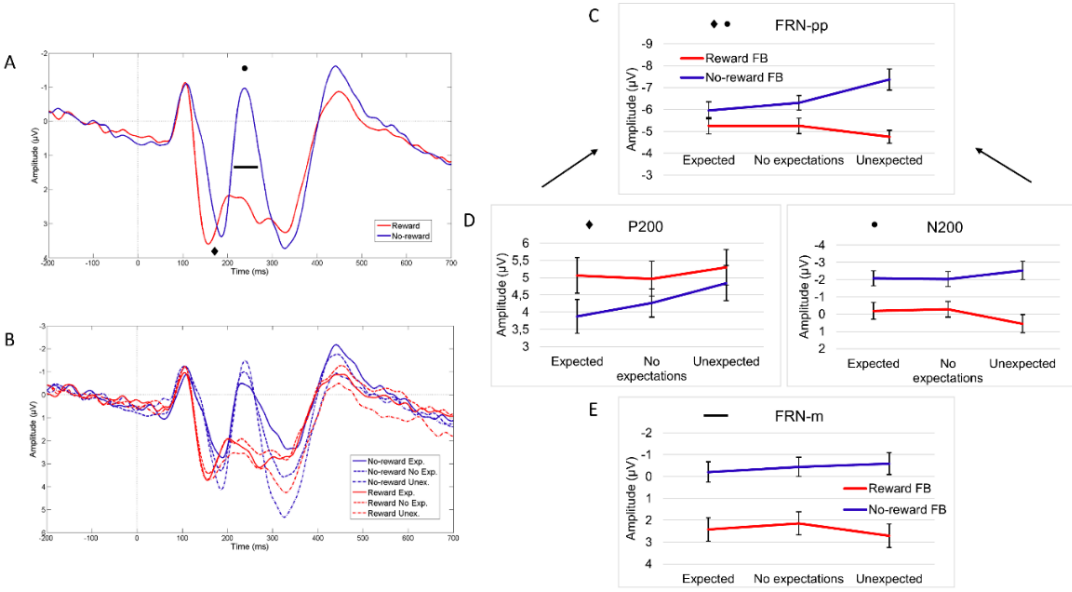

Figure 1. (A) Grand average ERP waveforms computed at FCz for reward and no-reward separately, collapsing across the three levels of FB expectation each time. A conspicuous N200 (giving rise to the FRN component) was elicited for no-reward FB, compared to reward FB. The diamond symbol refers to the preceding P200 (see Figure 1D – left panel for analysis of this component only). The dot symbol refers to the N200 proper (see Figure 1D – right panel for analysis of this component only). The small horizontal black line depicts the fixed interval used when the FRN is measured as mean amplitude (see Figure 1E). The FRN was analyzed using either peak to peak (FRN-pp, using the preceding P200 as initial peak – baseline, see Figure 1C) or as a mean ERP activity (FRN-m, see Figure 1E). (B) Grand average ERP waveforms computed at FCz for all six main conditions. At the N200 level, FB valence interacted with FB expectancy, whereby the N200 was the largest for unexpected negative FB. (C) Mean amplitudes of the FRN when computed peak to peak, showing a significant interaction between FB valence and FB expectancy. (D) Mean amplitudes for P200 (left panel) and N200 (right panel) alone. (E) Mean amplitudes of the FRN when computed using a mean amplitude measurement, showing a main effect of FB valence only. The error bar corresponds to 1 standard error of the mean.

4.3. Topographic Analysis.

Segmentation. Following the meta-criterion, a solution with sixteen different dominant maps was found to explain the ERP data set the best. The solution explained 93.71 % of the variance, see Figure 2. During the time window corresponding to the FRN and RewP, two different dominant maps were clearly evidenced. One map, sharing similarities with the FRN ERP component, showed a fronto-central negativity and started at a similar time point (i.e. 217 ms) regardless of feedback expectancy's level, but only for negative FB. Moreover this distinctive map was immediately followed by a different map showing a broader central positivity. This RewP-map was present and lasted until the same time point for all six FB types (i.e. 386 ms). The spatial correlation between these two maps was 0.84.

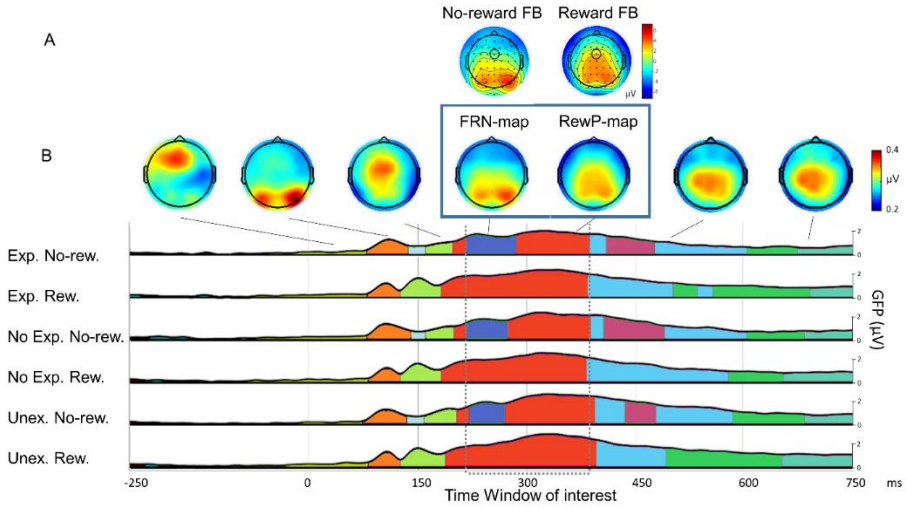

Figure 2. (A) Topographies (voltage maps) of the main ERP activities of interest (irrespective of expectancy), showing the RewP topography (left inset) and the FRN topography (right inset). The circle superimposed of the topographies corresponds to FCz electrode location. Each map is computed as the mean ERP activity during a 50 ms time interval around the N200 peak elicited by no-reward (see Figure 1A). (B) Outcome of the spatio-temporal segmentation of the grand average ERP data (with the six main experimental conditions considered, and showing the entire epoch starting 250 ms prior to and ending 750 ms after feedback onset). A solution with 16 different

topographical maps (where only 7 are actually depicted here) was found to explain 93.71 % of the total variance. During the time interval corresponding to the FRN/RewP components, two dissociable activities were evidenced based on FB valence. These two maps had different properties, including a longer duration for the reward-related one, and showed different sensitivity to FB expectancy (see Results section and Figure 3 for results after back fitting to individual subject ERP data).

Fitting. The extracted GEV and the mean correlation, provided by the fitting of the two dominant maps in the time window of interest (217 – 386 ms), revealed a significant main effect of map ($F(1, 43) \geq 9.04$, $p \leq .005$, $\eta 2 = .17$). Both variables showed a significant interaction between FB valence and map ($F(1, 43) \geq 34.47$, $p < .001$, $\eta 2 \geq .45$) and FB expectancy and map ($F(2, 86) \geq 7.86$, $p \leq .001$, $\eta 2 \geq .16$), see Figure 3. While the RewP-map explained more variance and showed a higher mean correlation for reward than no-reward FB ($M_{reward\text{-}meanCorr} = .70$, $SE = .02$, $M_{no\text{-}reward\text{-}meanCorr} = .63$, $SE = .02$, $p \leq .002$), the FRN map showed only a non-significant trend to fit better with the no-reward compared to the reward FB ($M_{reward\text{-}meanCorr} = .57$, $SE = .03$, $M_{no\text{-}reward\text{-}meanCorr} = .60$, $SE = .03$, $p \geq 0.25$). Regarding the GEV, both maps seemed to be sensitive to the expectancy manipulation as well. More variance was explained for the unexpected than the expected condition (FRN-map: $M_{unexpected} = .08$, $SE = .006$, $M_{expected} = .06$, $SE = .005$, $p \leq 0.05$). Especially the positivity map showed a steeper increase with unexpectedness (positivity map: $M_{unexpected} = .10$, $SE = .006$, $M_{expected} = .07$, $SE = .004$, $p < .001$). For the mean correlation, the RewP-map showed a similar pattern ($M_{unexpected} = .68$, $SE = .02$, $M_{expected} = .65$, $SE = .02$, $p < .015$), while the FRN-map did not differentiate between levels of expectancy ($M_{unexpected} = .58$, $SE = .03$, $M_{expected} = .58$, $SE = .03$, $p \geq 0.34$).

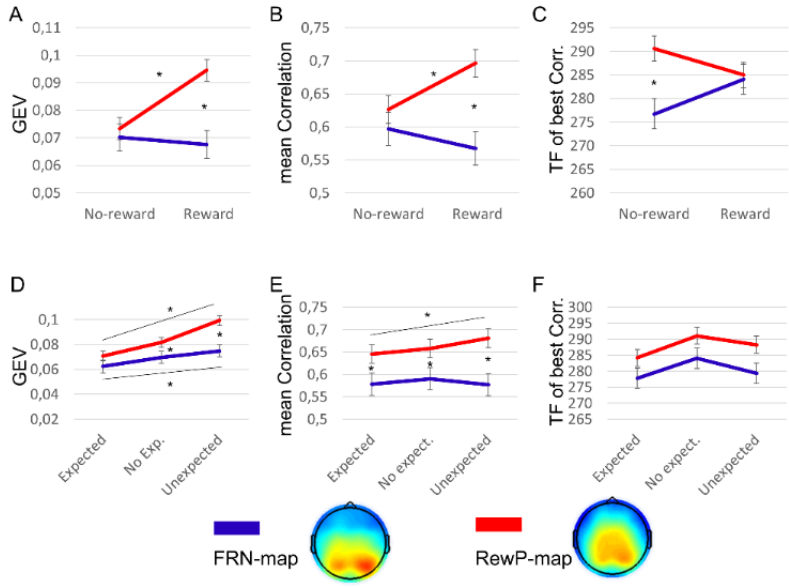

Figure 3. (A-F) Results obtained after fitting back the two dominant maps (FRN and RewP, regardless of expectancy) identified during the clustering step (see Figure 2B) during the 217-386 ms time interval following FB onset to individual subject ERP data, separately for the three main dependent variables used in this analysis: global explained variance (GEV), mean correlation and time-frame (TF) of best correlation. The error bar corresponds to 1 standard error of the mean. For each of them, a significant interaction effect between valence and map was found (A,B), explained by the generation of a reward-specific map for positive feedback, except for the TF of best correlation where a significant earlier time-course was found for the FRN-related map for negative feedback compared to the RewP map (C). (D-E-F) Results obtained after fitting showing differential effect of expectancy on the behavior of the two main maps. While the FRN-related map was weakly modulated by levels of expectancy, such an effect was clearly evidenced for the RewP map that showed a monotonic increase (in GEV or mean correlation) with increasing unexpectedness.

Importantly the TF of the best correlation for each map within this time large segment showed again a significant interaction between map and FB valence ($F(1, 43) = 8.31$, $p = .006$, $\eta 2 = .16$), indicating that for reward FB, both maps fitted equally well at 306 ms (MFRN-map = 305 ms, SE = 7.69, MRewP-map= 307 ms, SE = 6.04, $p = .81$), while for no-reward FB,

the FRN-map fitted the best much earlier than the RewP-map (MFRN-map = 277 ms, SE = 6.97, MRewP-map = 318 ms, SE = 5.79, $p < .001$). This result clearly indicated that the initial time window of interest (217 – 386 ms) was probably too broad and likely encompassed two dissociable processes in terms of spatial-temporal dynamic. To corroborate this assumption at the statistical level, we repeated the fitting within two short non-overlapping time windows lasting for 40 ms centered around 277 and 318 ms, respectively. The repeated measures ANOVA on the GEV values revealed, besides several significant main effects, two significant three way interactions between time-window, map and FB valence ($F(1, 43) = 66.37$, $p < .001$, $\eta^2 = .61$) and time-window, map and FB expectancy ($F(2, 86) = 5.01$, $p = .009$, $\eta^2 = .10$), see Figure 4. Whereas the FRN-map fitted the best in the early time window for no-reward FB (Mno-reward-early = .07, SE = .007, Mno-reward-late = .06, SE = .006, $p \geq .139$), the RewP-map fitted the best for reward FB in the later time window (Mreward-early = .07, SE = .006, Mreward-late = .10, SE = .006, $p \leq .059$). Furthermore, while the FRN-map did not vary with expectancy for none of the two time windows (Munexpected= .07, SE = .006, Mexpected= .06, SE = .006, $p \geq .139$), the positivity map showed this effect, especially in the later time window (Munexpected-late= .11, SE = .006, Mexpected-late= .08, SE = .005, $p \leq .003$). Using the mean correlation as fitting parameter, as opposed to the GEV, led to a similar statistical outcome.

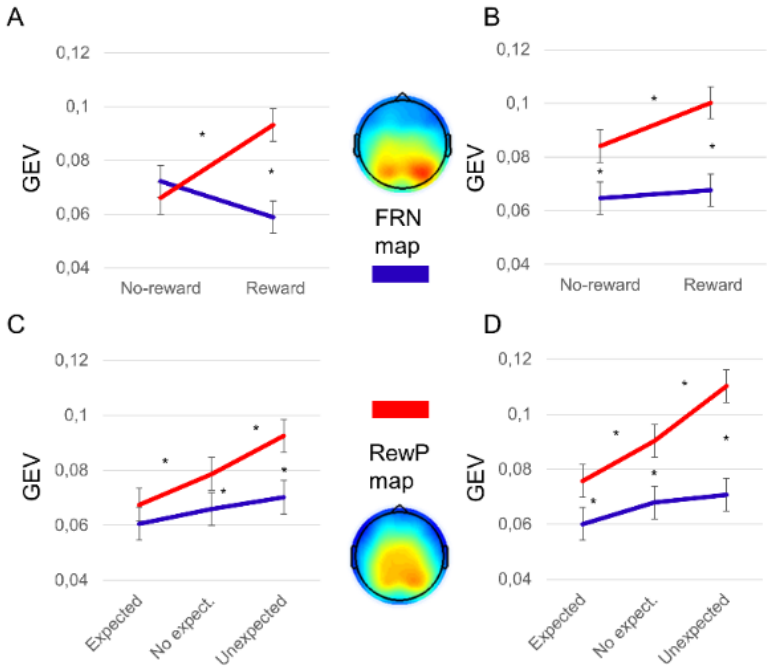

Figure 4. Fitting results (GEV only) shown separately for the early (left column) and late time-window (right column) identified by the main analysis (see Results section for details). Whereas the FRN-map discriminated better no-reward from reward FB during the early time interval (A), the RewP-map discriminated better reward from no-reward FB during the later time interval (B). (C) The FRN-map did not vary with expectancy (in none of the two time intervals). (D) By comparison, the RewP-map varied with expectancy, especially during the later time interval. The error bar corresponds to 1 standard error of the mean.

4.4. Source Localization.

The statistical comparison in the inverse-solution space between reward an no-reward within the time window of the FRN- and RewP-map (217-386 ms) revealed two non-overlapping suprathreshold (t value > 4.13, corrected for multiple comparisons) clusters showing opposing reward-related effects, see Figure 5. One cluster, being more active for

no-reward than reward FB, was located within the dACC, including Brodmann area (BA) 32; (maximum at 15x, 25y, 40z, t(43) = -5.31, p < .001) and spreading to adjacent frontal areas, including BAs 6, 8 and 9. The other non-overlapping cluster showed the opposite pattern (more active for reward than no-reward FB) and was located in the posterior cingulate cortex (PCC; BA 23; maximum at -5x, -60y, 15z, t(43) = 5.85, p < .001), extending to adjacent (medial) parietal regions (such as the Precuneus or retrosplenial cortex; BA 31), as well as more ventrally to the posterior part of the Parahippocampal gyrus (BA 27). It also spread to the posterior part of the left insula (BA 13; max. at -30x, -40y, 20z, t(43) = 4.89, p < .001).

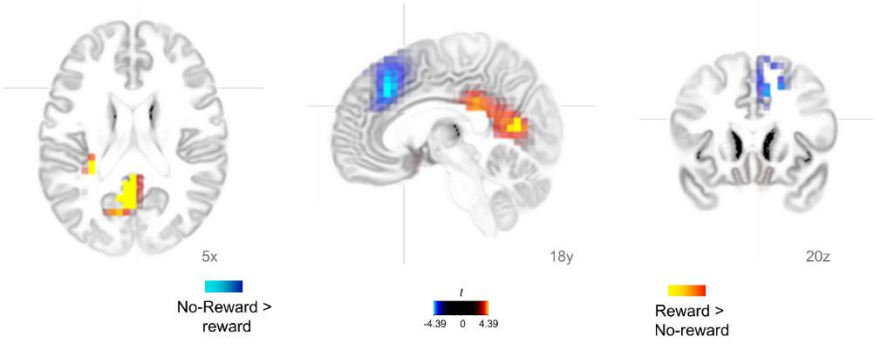

Figure 5. Source localization results. Hot colors provide activations (corrected for multiple comparisons, see Results section for details) for the contrast between reward and no-reward FB, while cold colors provide suprathreshold activations for the reverse contrast. These statistical maps were generated for the mean ERP activity generated within the 217-386 ms time interval following FB onset. No-reward compared to reward yielded activation in the dACC (BA 32; see right inset), spreading to nearby frontal areas (BAs 6, 8, and 9). Conversely, reward compared to no-reward led to activations in the PCC (BA 23; see left inset), spreading to parietal and more ventral regions, including the Precuneus and Parahippocampal gyrus (BAs 23, 27, 29, 30, 13, and 18). It also extended to the left posterior insula (BA 13).

5. Discussion

RPE signals recorded at the electrophysiological level during PM are thought to provide an integration of expectancy and valence of the outcome, such that a differential response to rewarding vs non-rewarding outcome increases as a function of its unpredictability (Holroyd and Coles, 2002; Schultz et al., 1997). If the evidence for a mismatch between expectation and outcome is motor based (e.g., clear response error), then such an effect can be tracked at the level of response-locked ERPs, such as the ERN. However, if the evidence cannot be computed at the response level (e.g., during gambling or probabilistic learning), then FB provides the main source of information to estimate RPE, with neurophysiological effects visible at the level of the FRN/RewP. The present study focussed on this latter effect. More specifically, we aimed to characterize the topographical properties of the FRN component, when compared to the RewP, in order to assess whether they share common or instead dissociable topographic variance and neural generators. Importantly, we could compare the outcome of this data-driven method (taking into account all electrodes and time-frames) to two standard ERP scoring methods available in the literature, focussing on a circumscribed time-window and FCz electrode only.

To this aim, 44 participants carried out a previously used gambling task (Hajcak et al., 2007; Paul and Pourtois, 2017), where FB valence and expectancy were manipulated on a trial-by-trial basis, while 64-channels EEG was recorded concurrently. This enabled us to estimate the contribution of these two independent variables to systematic changes in the ERP signal following FB onset, when it corresponded either to amplitude modulations recorded at FCz only, or alternatively, when considering the spatial configuration of the entire electric field (i.e., topography). A number of new results emerge from the current study. (i) When comparing two different, albeit standard, scoring methods for the

FRN in the existing ERP literature, our results show that this component was reliably modulated by FB valence and expectancy when using a peak to peak measurement only (FRN-pp, i.e., measuring peak amplitude of the N200 relative to the preceding P200 at FCz component). Importantly, a similar outcome was reported when measuring the N200 alone. By comparison, when we used a more stringent mean amplitude measurement at the same lead (FCz) (FRN-m, i.e., measuring FRN as a mean ERP activity spanning from 213 to 263 ms interval centered around the N200 peak), it was modulated by valence without significant change by expectancy, suggesting in turn a dissociation between them. (ii) These somewhat inconsistent results were supplemented with a topographical pattern analysis that strongly reduced the number of priors in terms of location and latency for identifying reward-related effects following FB onset, and possible interactions with expectancy. This analysis suggested the existence of two dissociable topographies during the time-interval corresponding to the FRN and RewP. A main topography characterized by a short-lasting prefrontal negative component was generated relatively early after negative FB onset and was somehow independent from its expectancy. Another one showed a broad positivity at more central and parietal sites during the same early time interval, and was generated in response to reward. Crucially, this latter reward-related topography lasted longer and best represented the variance of the ERP signal in a later time window, where it also varied systematically as a function of reward expectancy, accounting for more variance for unexpected than expected positive FB, in agreement with the tenets of the dominant RPE framework (Schultz, 2013). Given these specific electrophysiological properties and opposing sensitivity to FB valence, we tentatively linked the first one to the FRN and the second one to the RewP, when corresponding to local amplitude variations of specific deflections measured at a single scalp channel. Because different topographies necessarily denote non-overlapping intracranial generators (Lehmann and Skrandies, 1980;

Michel and Murray, 2012; Vaughan, 1982), we estimated their sources using a linear inverse solution algorithm (sLoreta, see Pascual-Marqui, 2002). While the FRN-compatible topographical activity had a main cluster within the dACC, the RewP-one was source localized to a distributed and extended network, comprising primarily the PCC. Below, we discuss the implications of these new results, and eventually formulate some recommendations for the definition and use of feedback-based reward-related ERP activities in future studies.

At FCz scalp location, independently of the scoring method adopted and actual definition used for the ERP component of interest (either local amplitude changes or topography), we consistently found across these different methods used that the FRN amplitude varied reliably with valence, i.e. it was consistently larger for no-reward than reward FB, while conversely, the RewP amplitude was systematically larger for reward than no-reward FB. Noteworthy, the FRN component was sensitive to FB expectancy only when using a peak to peak analysis (FRN-pp). Thus the peak to peak scoring method was the only one with which the FRN was found to be coherent with the generation of a dopamine-dependent RPE signal (Holroyd et al., 2003; Holroyd and Coles, 2002; Schultz et al., 1997; Ullsperger et al., 2014b). No such modulation was found for the RewP, no matter which ERP scoring method was actually adopted. In light of the existing debate in the ERP literature about the sensitivity of the FRN, or instead RewP to FB expectancy (bearing in mind that these two hypotheses are not necessarily mutually exclusive and are both consistent with the original FRN-RL theory; see Holroyd et al., 2008; San Martín, 2012), our results lend support to the classical FRN hypothesis (Holroyd and Coles, 2002; Ullsperger et al., 2014b; Walsh and Anderson, 2012).

When the FRN was scored as mean amplitude around the peak of the N200 (FRN-m), no reliable modulation by FB expectancy was found. This inconsistency across the two scoring methods might be explained by several factors. On one hand, the peak to peak measurement may have

artificially inflated the component's amplitude due to noise in the data (Luck and Gaspelin, 2017). On the other, scoring the FRN using the mean amplitude computed for a relatively long and pre-defined time window, albeit being a more conservative approach that is less sensitive to noise in the measurement, might have overshadowed an effect of expectancy due to inter-individual variability in the latency (and morphology) of the P200-N200-P300 complex, and/or to the possible temporal overlap of the N200 with the preceding P200 and/or the following P300. The N200 is usually flanked by these two positive components, which usually do show amplitude modulations with stimulus frequency, and thus expectancy (Donchin and Coles, 1988; Polich et al., 1996), although with an effect going in the opposite direction compared to the N200. Neglecting these features of the ERP signal can in turn potentially smear amplitude effects which are small in size, such as the expectancy effect on the FRN. Indeed, the peak to peak approach (FRN-pp, where preceding P200 is used as baseline peak for N200 peak measurement) was put forward as an alternative scoring method to control for this confounding effect (Holroyd et al., 2003; Sallet et al., 2013). Notably, by further exploring amplitude modulations brought about by FB expectancy (and valence) for each deflection separately (i.e., P200 and N200), we could confirm that the significant interaction effect between FB valence and FB expectancy at the N200 level (hence FRN) was not merely resulting from the preceding P200 (see Results). As a rule of thumb, depending on the experimenter's goal and research interest, one of the two scoring methods could be preferred above the other one. For instance, if the focus is on reward itself, the use of the FRN-m appears warranted. By comparison, if more subtle influences of expectancy are explored at the FB (and FRN) level, then a FRN-pp scoring method appears more appropriate than the FRN-m. However, in light of these slight discrepancies between the different scoring methods used, and for comparison purposes with previous work in the literature, it appears important to report and compare the outcome

of these different scoring methods when it comes to assessing the sensitivity of an ERP component, like the FRN or RewP, to FB valence and expectancy.

Although these classical peak analyses informed about the complex interplay between reward and expectancy during feedback-based PM, yet they are necessarily based on local amplitude variations only (here measured at FCz), and as such, they could therefore potentially overlook more global changes in the ERP signal occurring with these two factors, including topographical alterations. To explore this possibility, we supplemented these analyses with a topographical ERP mapping analysis that considered the FB-locked ERP signal when measured at all (64) electrodes concurrently, and during a large time interval following FB onset (hence, not restricted to local peaks or maxima only), reducing in turn strongly the number of priors. This analysis confirmed the presence of a clear topographical change depending on actual FB outcome during the time interval usually associated with the FRN or RewP. Whereas a main topography shared many similarities with the FRN component (no-reward dominance), the other competing spatial configuration of the electric field closely resembled what is usually referred to as RewP in the existing ERP literature and showed enhanced activity for reward. Moreover, source estimation using sLoreta confirmed the presence of two non-overlapping networks accounting for these two dissociable maps. As predicted by many models and earlier ERP studies (Bush et al., 2000; Fouragnan et al., 2015; Gehring and Willoughby, 2002; Miltner et al., 1997; Shackman et al., 2011; Ullsperger et al., 2014b), we found that the dACC provided the main intracranial generator of this FRN-compatible map. In comparison, the RewP activity was source localized to more posterior regions, including the PPC, an area known to be involved in reward processing (Knutson et al., 2001; Liu et al., 2011; Luu et al., 2003; Nieuwenhuis et al., 2005). Even though some caution is needed in the interpretation of these source localization results (as they correspond to imperfect mathematical

reconstructions of the intracranial sources), this dissociation along the cingulum depending on FB valence is not odd, but very much in line with the taxonomy of functionally-distinct sub-regions composing it, as previously put forward by Vogt (2005). In this framework, the anterior midcingulate cortex (aMCC) is linked with the processing of negative emotions (and the need for cognitive control, see Shackman et al., 2011), especially fear, anxiety, and even pain. Conversely, the PCC is assumed to play a predominant role in attention control, especially in orienting to targets that are potentially of high motivational value for the individual, in integrating the history of rewards previously experienced, as well as in the assessment of personal relevance of incoming (emotional) information, and controlling the balance between internal and external attention (Leech and Sharp, 2014). Using this neuro-anatomical framework, we could thus conjecture that the stronger aMCC response to no-reward FB in our study might reflect an (whole or none) alarm or alert signal in case the outcome turns out to be relatively "negative" (no-reward) (Shackman et al., 2011). In comparison, the stronger PCC activation to reward FB seems consistent with an attentional orienting effect towards an approach-related or motivationally significant event for the participant, namely getting a small financial reward after gambling in the present case. Similar interpretations of related findings have been drawn in the context of error monitoring (Paul et al., 2017) and reinforcement learning (Fouragnan et al., 2015).

Turning to the possible changes of these global ERP activities with FB expectancy, our topographical analysis additionally showed a striking modulation that none of the two classical ERP analyses (using FCz only) could actually reveal. Not only was FB valence clearly modulating the expression of the global electric field, but FB expectancy influenced its expression as well and in a condition-specific manner. As our analysis revealed (see Figure 2), the RewP-related map appeared to be the default ERP activity somehow in this long interval (from 210 to 380 ms following FB onset), progressively building up across this specific interval and

reaching its maximum at ~320 ms following FB onset. No-reward outcome turned out to "break up" this default processing at an early latency (~280 ms following FB onset), with the generation of a unique and distinctive topography (being also short-lived), namely the FRN map. This result supports the idea that in case of a "negative" event (here corresponding to the lack of reward), a phasic negative ERP activity similar to the N200-component (Heydari and Holroyd, 2016; Shahnazian and Holroyd, 2017) is elicited, which temporarily overrides the standard (reward-driven) ERP response. Although remaining largely speculative, this break-up effect might be caused by a phasic dip or transient pausing in dopaminergic firing, as the RL-theory would suggest (Fiorillo et al., 2003; Schultz, 2013; Warren and Holroyd, 2012). At variance with this interpretation, a positivity associated with better than expected positive outcome (Proudfit, 2015) could have been overridden by a more generic brain response to salient events in general (Holroyd et al., 2008; Talmi et al., 2013). Importantly, in line with the FRN-m analysis, this FRN-compatible topographical map did not show however a systematic modulation (in explained variance) with expectancy. We may speculate that both the FRN-m and the topographic mapping for the FRN map overlook a phasic, short-lived, local modulation of expectancy that only the FRN-pp and the N200 peak analyses were able to capture. Such a modulation was well evidenced in our topographic ERP mapping analysis, but for the RewP-related topography and at a later time point, however. Accordingly, these topographical results inform about the actual spatio-temporal dynamic of reward processing, suggesting that early on following FB onset, FB valence mostly influenced the expression of the ERP signal (irrespective of expectancy). In the present case, this FB valence effect was characterized by the transient blocking of the (normal) reward-related activity and replacement for a short period of time by another, negative or loss-related, ERP activity sharing many similarities with the FRN. Because our ERP results suggest the existence of two separate and dissociable networks depending on actual FB valence (yet

having both an early time-course following FB onset), they clearly speak against the use of difference waves, where a new and undefined ERP activity would likely be created as a result of this transformation, in case no-reward would be subtracted from reward FB for example. Such an approach, although possibly reducing the number of factors/variables included in the statistical analysis (Luck and Gaspelin, 2017), would nonetheless overlook and mitigate the existence of independent sources and effects that each contributes to both (local) amplitude as well as (global) topographical changes in the ERP signal following FB onset. Hence, a clear methodological implication of our new ERP results is that the use of difference waves should not be recommended as it could blur or smear important differences between the processing of reward vs. no-reward outcome during PM.

As mentioned above, we succeeded to evidence systematic modulations of the feedback-locked ERP signal with expectancy with the elected topographic ERP mapping analysis. They were found for the RewP-related map exclusively, and became stable at the statistical level when considering a later time interval following FB onset (compared to the FRN map). Interestingly, the PCC and adjacent areas which are thought to give rise to this ERP activity, has previously been shown to be involved in detecting novel, or unpredicted events (Gabriel et al., 2002; Mccoy et al., 2003). Moreover, earlier ERP studies already clearly showed that during a comparable time window following FB onset, the amplitude of the RewP was modulated by expectancy and hence RPE (Sambrook and Goslin, 2015; Talmi et al., 2012). Accordingly, given this clear modulation of the ERP signal with expectancy for the RewP-related map, our novel results lend indirect support to earlier studies and models available in the ERP literature that posited that effects of expectancy on the FRN component might very well be driven in part by responses to unexpected reward as well (Holroyd et al., 2008; Walsh and Anderson, 2012). Yet, this effect was found when considering the topography only, and a relatively

late time interval (i.e., 298-338 ms following FB onset). Although we failed to find evidence of a systematic change in the explained variance of the FRN-compatible topography with FB expectancy, some cautious is needed in the interpretation of this "null" result. For example, it remains to be tested whether using monetary loss or punishment for the no-reward outcome might not yield stronger modulations of the FRN-compatible topography with expectancy, as this manipulation would necessarily increase the salience of the no-reward outcome (Esber and Haselgrove, 2011). Accordingly, whether or not the FRN-compatible topography varies (in explained variance) with expectancy awaits additional empirical work where other contrasts at the outcome level should be used and compared systematically using similar ERP methods (including loss-related ones and hence the activation of a defensive motivational system; Hajcak and Foti, 2008). Notwithstanding this caveat, our new topographical ERP results are important because they clearly suggest that the processing of FB valence during gambling may obey a two-stage process: first FB valence is evaluated (with no-reward interfering with the default reward-related ERP activity apparently), before a strong expectancy effect comes into play during a later stage and dynamically shapes reward processing, selectively. Presumably, this modulation might reflect the assignment of a different motivational value to the reward-related FB depending on its expectancy. This interpretation aligns well with recent neurophysiological evidence that reveals a specific temporal sequence during evaluative FB processing (Fouragnan et al., 2015; Philiastides et al., 2010): the early (around 220ms post FB onset) categorical evaluation of the outcome (i.e. valence) is later followed (around 300ms) by the processing of its actual deviation relative to the expectation (i.e. salience). More generally, such rapid and fine-grained changes in the actual spatio-temporal dynamic of reward processing during PM could hardly be captured by means of a standard ERP data analysis. Hence, we contend that future ERP studies focused on reward processing and PM should better incorporate this

important feature of any ERP component (FRN, RewP, P200, P300 or N200), namely the topography, as it carries relevant information about the complex interplay between FB valence and expectancy. This approach might also help to revise or amend some of the current models available in the field that directly use these specific ERP components to generate testable predictions about the neurophysiology of reward processing and PM (Ullsperger et al., 2014b).

Despite its apparent strengths and added value, some limitations related to this topographic ERP mapping analysis warrant comment. Because this approach is based on an estimation (and clustering) of the dissimilarity in terms of spatial configuration of the electric field across successive TFs, it is not suited to reveal the contribution of putative independent components/sources that would be active and compete with one another at the exact same time, for which an ICA or PCA (Foti et al., 2015, 2011; Proudfit, 2015) should preferably be used for example (Eichele et al., 2010). Previously published findings (Holroyd et al., 2008; Proudfit, 2015) suggested that the ERP responses to reward and loss mostly differ by means of a positivity that is unique to reward trials, as opposed to a negativity to no-reward ones. By comparison, the outcome of our ERP topographic mapping analysis suggests the presence of a phasic FRN-map (characterized by a fronto-central negativity) generated in an early time window following no-reward (around 277ms), which seems to overlap and interfere with a longer-lasting reward-related activity (characterized by a positivity showing a centro-parietal scalp distribution). Tentatively, this discrepancy between our current and these previous ERP studies could be related to the abovementioned methodological factors, as well as the actual incentive used to guide performance monitoring (being sometimes either primarily reward-related or instead loss-related). Presumably, for these reasons our topographic ERP mapping analysis failed to reveal a specific (short-lived) topography associated with reward outcome that would mainly be characterized by a central positivity

culminating when the N200 (no-reward) reached its maximum amplitude, as previously suggested for the RewP ERP component (Novak and Foti, 2015; Proudfit, 2015). The RewP topographical map revealed in our study showed instead a broader (central and posterior parietal) and longer-lasting positivity that presumably partly overlapped with the P300 component. Therefore, it remains to determine to which extent the RewP map found in our study corresponds to the RewP ERP component exclusively, or also encompasses the P300 component. Last, it would also be beneficial in future studies to assess whether these two different topographies identified here may also be related somehow to different variations in the spectral content of the EEG/ERP, as recently reward processing has been associated with systematic changes in the power of either theta or delta oscillations (Bernat and Nelson, 2008; Cohen et al., 2007; Marco-Pallares et al., 2008). Considering the ERP results obtained with the different scoring methods used in our study (FRN-m, FRN-pp, or N2 peak) and some dissociations found between them, it appears challenging to relate complex cognitive processes, such as expectancy or reward, to single and temporal-specific ERP deflection, such as the P2 or N2. In this context, a better understanding of the actual neurophysiology of these complex cognitive processes could probably be achieved by supplementing classical ERP analyses with time/frequency methods that can inform about the actual spectral content of the P2-N2-P3 complex, its modulation by reward and expectancy (Cavanagh et al., 2012, 2010; Cohen et al., 2007; Cohen and Donner, 2013; Mas-herrero and Marco-pallarés, 2014; Paul and Pourtois, 2017), and the relative role of phase locked (captured by ERPs) and non-phase locked oscillatory activity in explaining these effects (see also Cohen and Donner, 2013; Hajihosseini and Holroyd, 2013).

In summary, the current ERP results advance our understanding of reward processing during gambling (in healthy adult participants) and more specifically how reward is actually shaped by expectancy when the

topography, as opposed to amplitude measurements performed at a single scalp location, is carefully considered and properly analysed. Our new results lend support to the existence of two – spatially and temporally – dissociable networks during FB processing. One is driven by no-reward and comprises the dACC, meeting many of the electrophysiological criteria used previously to define the FRN component in the extant ERP literature. The other one competes with the first one, and is primarily reward-related (as well as sensitive to expectancy), sharing in turn many similarities with the RewP. Since abnormal reward processing (and anhedonia) is a cardinal diagnostic feature of several affective disorders, such as major depression, addiction, schizophrenia or pathological gambling, the topographic ERP mapping analysis performed in this study, and meant to explore thoroughly the spatio-temporal dynamic of reward processing during PM, could be used more systematically in the future in clinical settings to elucidate which component of reward processing, in relation to expectancy, could be impaired in these patients.

6. References

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Chapter 3: Integration of reward with cost anticipation during performance monitoring[1]

[1] Gheza, D., De Raedt, R., Baeken, C., & Pourtois, G. (2018). Integration of reward with cost anticipation during performance monitoring revealed by ERPs and EEG spectral perturbations. NeuroImage, 173, 153–164.

1. Abstract

Effort expenditure has an aversive connotation and it can lower hedonic feelings. In this study, we explored the electrophysiological correlates of the complex interplay of reward processing with cost anticipation. To this aim, healthy adult participants performed a gambling task where the outcome (monetary reward vs. no-reward) and its expectancy were manipulated on a trial by trial basis while 64-channel EEG was recorded. Crucially, on some trials, the no-reward outcome could be transformed to a rewarding one, pending effort expenditure by means of an orthogonal dot clicking task, enabling us to compare at the electrophysiological level reward processing when cost was anticipated or not. We extracted and compared different markers of reward processing at the feedback level using both classical ERPs and EEG spectral perturbations in specific bands (theta, delta and beta-gamma). At the behavioral level, participants reported enhanced pleasure and relief when the outcome was rewarding but effort expenditure could be avoided, relative to a control condition where the outcome was rewarding but no extra effort was anticipated. In this condition, EEG results showed a larger Reward Positivity ERP component and increased power in the Delta and Beta-gamma bands. By comparison, cost anticipation did not influence the processing of the no-reward outcome at the FRN and frontal midline theta levels. All together, these neurophysiological results suggest that effort avoidance is associated with increased reward processing.

2. Introduction

Humans tend to obey to a principle of economy ("law of less work"; Hull, 1943). This principle applies to both physical and cognitive effort (Apps et al., 2015; Kool et al., 2010), whereby rewards are devalued by the cost required to obtain them (Charnov, 1976; Salamone et al., 2007). An increasing interest on motivational and emotional processes underlying decision making, where the integration of effort with reward occupies a central place, has been witnessed recently in a wide range of disciplines, spanning from neuroeconomics (Westbrook and Braver, 2015) to psychopharmacology (Salamone et al., 2012) and neuroscience (Apps et al., 2015; Chong et al., 2017; Ma et al., 2014; Vassena et al., 2014). These valuable efforts have substantially advanced our understanding of how motivation shapes decision making, especially from a computational perspective that provides mechanistic accounts to explain brain mechanisms responsible for value processing and effort deployment (Holroyd and McClure, 2015; Kurzban et al., 2013; Vassena et al., 2017; Verguts et al., 2015). In this literature, the dorsomedial and dorsolateral prefrontal cortex are often considered as domain-general brain regions involved in reward (d)evaluation when encountering either cognitive or physical effort (Chong et al., 2017). In particular, the anterior cingulate cortex (ACC) and the striatum are thought to signal effort anticipation (Kurniawan et al., 2013, 2010), and to process the expectation of both reward and cognitive effort (Vassena et al., 2014). At the electrophysiology level, neural activity arising from the ACC has traditionally been related to specific performance monitoring (PM) or cognitive control (CC) ERP components, such as the ERN (Error related negativity) and FRN (Feedback related negativity; see Holroyd and Coles, 2002). PM is a complex ability relying on different and interconnected mental processes, including an early evaluative component, in case errors or mismatches are detected and need to be rapidly processed to foster goal-adaptive behavior. At the electrophysiological level, this early evaluative component

has been related to specific EEG markers, elicited both in the time and time-frequency domains (Ullsperger et al., 2014b).

In the time-domain, the FRN component is usually defined as a negative ERP deflection peaking at around 250ms at channels FZ or FCZ after evaluative feedback (FB) onset. FB is characterized as evaluative since it provides information about performance outcome in the present case. FRN's amplitude is enhanced after negative vs. positive, and unexpected vs. expected FB, thus providing an electrophysiological marker of PM sensitive to both outcome expectation and valence information (Holroyd and Coles, 2002; Ullsperger et al., 2014a; Walsh and Anderson, 2012). Traditionally, the negative deflection (i.e. N200) giving rise to the FRN has been linked to a phasic and signed reward prediction error (RPE) signal (Holroyd and Coles, 2002). More specifically, it conveys the direction of the deviation between the actual and the expected outcome. This phasic signal is thought to be generated first in deep dopamigeric structures (midbrain), before it is relayed to the medial prefrontal cortex, including the ACC which is thought to provide the main intracranial generator of the FRN. Whereas dopamine has usually been put forward as the main neurotransmitter accounting for RPE in the context of reinforcement learning and PM, more recently, other neurotransmitter systems have also been considered in this process. These include norepinephrine (Riba et al., 2005) and the involvement of the locus coeruleus in decision-making (Aston-Jones and Cohen, 2005), GABAa (reducing the amplitude of the ERN; De Bruijn et al., 2004), but also serotonin and adenosine (for a review see Jocham and Ullsperger, 2009). The cognitive processes giving rise to PM, its neural underpinning as well as its electrophysiological signature, are still debated in the current literature. For instance, with regard to the FRN, the ERP amplitude difference between negative and positive FB has been interpreted as a positivity associated with better than expected outcome (Eppinger et al., 2008; Holroyd et al., 2008; Holroyd and Umemoto, 2016; Sambrook and

Goslin, 2014). Accumulating evidence indicates that such an outcome-dependent amplitude difference may be driven by sensitivity to rewarding rather than non-rewarding events (Arbel et al., 2013; Baker and Holroyd, 2011; Foti et al., 2011; Potts et al., 2006; Sambrook and Goslin, 2014; Weinberg et al., 2014), leading thereby some authors to name this ERP component Reward Positivity (RewP; for a review, see Proudfit, 2015), as opposed to FRN. Although sharing some similarities at the electrophysiological level, the FRN and RewP usually show non-overlapping scalp distributions (i.e. topography), suggesting the existence of partly dissociable neural systems giving rise to them, as we recently confirmed (Gheza et al., 2017).

Evaluative FB processing during PM also influences non-phase locked EEG activities that cannot be captured using a standard ERP analysis (Cohen, 2014). Among them, frontal midline theta (FMT, 4-8 Hz) measured at the same recording sites as the FRN and during a similar time window (~200-400 ms post-feedback onset) corresponds to a slow oscillation aggregating mostly the phase-locked activity reflected by the FRN (as well as its neighboring positivities, such as P2 and P3) as well as a non-phase locked (induced) component (Cohen and Donner, 2013; Hajihosseini and Holroyd, 2013). Unlike the FRN which has been put forward as a signed RPE signal (Holroyd and Coles, 2002; Ullsperger, 2017), FMT is thought to reflect an unsigned electrophysiological signal that captures dynamic interaction effects between medial frontal cortex (including ACC) and lateral prefrontal areas. Compatible with this view, its power is usually enhanced when cognitive control is needed (Cavanagh et al., 2010; Cavanagh and Shackman, 2015; Cohen et al., 2007; Cohen and Donner, 2013; Hajihosseini and Holroyd, 2013), or higher cognitive effort and task demands are required (Mussel et al., 2016; Wascher et al., 2014). Besides this cognitive control signal represented by FMT, evaluative FB processing usually influences the spectral content of the EEG signal in at least two other non-overlapping bands. The power in the

Delta band (0 - 4 Hz), measured at central and posterior-parietal sites, usually increases for rewarding compared to non-rewarding conditions (Webb et al., 2017). Last, in the Beta-gamma range (from 20 to 35 Hz) at fronto-central sites, (monetary) reward is also associated with increased power (Cohen et al., 2007; Marco-Pallares et al., 2008; Mas-Herrero et al., 2015). The link between power changes in Beta-gamma activity and reward was substantiated by studies showing effects of reward probability (HajiHosseini et al., 2012) and reward magnitude (Marco-Pallares et al., 2008) in this specific frequency band.

Whereas feedback valence and expectation strongly influence the expression of these different feedback-based electrophysiological effects (Ullsperger et al., 2014a), as reviewed above, it is nowadays much less clear to which extent the cost associated with effort anticipation also does, and if so, for which of them and in which direction. Specifically, to which extent the evaluation of a given outcome is shaped by effort anticipation has never been investigated at the electrophysiological level. This paucity is somewhat surprising given that effort is profoundly linked to reward processing. As mentioned above, recent theoretical models advocate their integration in decision making, both in animals (Salamone et al., 2012, 2007, 2003) and in humans (Apps et al., 2015; Kool et al., 2010), corroborating the assumption that PM, and more generally CC, might exploit specific incentive signals or values where both reward and effort/cost have been integrated with one another. In particular anticipated reward and effort rely on a similar cortico-limbic network (Vassena et al., 2014), and are integrated (at the ACC level) during decision making so that the value of an option decreases as a function of associated effort (Croxson et al., 2009; Prévost et al., 2010). These studies suggest that reward processing during PM may be influenced by effort or cost, and more specifically its prospect or anticipation. Moreover, according to some recent models (Pizzagalli, 2014), the most prevalent emotional illness in Western developed countries, namely Major Depressive Disorder (MDD),

is thought to be associated with abnormal dopaminergic (DA) signaling in specific corticostriatal networks. Yet, these alterations do not seem to affect hedonic reactions per se (i.e. "liking"; Berridge et al., 2010; Salamone et al., 2007). Instead, they appear to alter incentive salience and reward learning (Admon and Pizzagalli, 2015; Whitton et al., 2016), in interaction with an abnormal stress reactivity (Pizzagalli, 2014). This impairment might also account for the blunted motivation to approach rewarding or pleasurable stimuli (wanting) in these patients, or alternatively engage effort to do so (Salamone and Correa, 2012; Treadway et al., 2012). Further, according to a recent neuro-computational model (Holroyd and McClure, 2015; Holroyd and Umemoto, 2016) the ACC, which provides the main generator of the FRN and FMT oscillations (Smith et al., 2015), is deemed responsible for selecting and motivating extended behavior (see also Holroyd and Yeung, 2012). The ACC would serve as the main node within a hierarchical neural system that translates reward evaluation into CC, implemented in dorsolateral prefrontal areas. Following this model's tenets, control signals in the form of FMT oscillations may be generated at the ACC level, as a function of both the learned value and the effort required by the selected, reinforced behavioral response. In this study, we sought to test these predictions, and assess the extent to which the different electrophysiological components described above could show systematic amplitude variations depending on cost anticipation. More precisely, FMT was expected to increase during the anticipation of effort, due to its putative role in signaling the need for increased control to dorsolateral prefrontal areas, which ultimately coordinate and implement the appropriate behavior. On the other hand, the main ERP components of reward processing (FRN and/or RewP) which are generated in the ACC, might therefore also capture a rapid integration of reward with effort or cost anticipation, given that previous neuroimaging studies pinpointed the ACC as one of the brain regions

where this integration took place (Chong et al., 2017; Kurniawan et al., 2013; Vassena et al., 2014).

To this aim, we capitalized on a previously validated gambling task (Hajcak et al., 2005; Paul and Pourtois, 2017) allowing to manipulate on a trial by trial basis FB outcome (either reward or no reward) and reward expectation (being high, intermediate or low) in a factorial design, and eventually measure clear-cut FMT power, FRN, RewP components as well as centroparietal Delta and Beta-gamma power changes elicited by evaluative FB. Critically, we added a new experimental condition to this paradigm (here below referred to as "special trials") where participants were occasionally invited to redo the gamble in case the outcome turned out to be "no reward" (with the hope for them to transform this no-reward event into a rewarding one). However and noteworthy, in this condition, if they freely decided to do so, they actually had to perform another unrelated task (before being allowed to actually redo the gamble) that clearly included effort expenditure, namely a random dot clicking task (for a similar approach, see Klein et al., 2005; Sherdell et al., 2012; Treadway et al., 2012). Importantly, information about the possibility to redo the gamble (or not) was always provided to participants at the beginning of each trial to activate a specific motivational set throughout the trial (i.e., anticipated cost). After extensive piloting (see Methods and Supplementary Materials – Table 1), we devised specific parameters for this additional dot clicking task to provide an optimal tradeoff between effort and reward for our current research goals: preferably, (healthy adult) participants would most of the time choose to redo the gamble (with the goal to win a small monetary reward) despite the need to carry out this orthogonal effort-based clicking task, allowing us to explore reward processing when cost was anticipated or not. Because cost anticipation here refers to the effort required by the additional task, as well the time and mental resources allocated to its execution, it also relates to opportunity cost (Kurzban et al. 2013). This way, we were able to

eventually compare evaluative feedback processing between two conditions that were carefully matched along all possible dimensions (e.g., stimulus properties, actual choice and reward probability), but differed regarding cost anticipation (being present or absent). Based on the literature reviewed above, we formulated different predictions. (i) We surmised a lower FRN for no-reward outcome that could be redone (special trials), compared to the same outcome without this possibility being offered (regular trials), in line with the putative link assumed between this specific ERP component and RPE (Holroyd and Coles, 2002). In other words, the (motivationally relevant) prospect of changing a negative into a positive outcome, albeit requiring extra efforts, would lead to less negative valence, compared to the same condition where no such change could be achieved. (ii) In agreement with the Hierarchical reinforcement learning theory outlined above (Holroyd and Umemoto, 2016), FMT power, being closely related to CC, should increase for no-reward outcome in the special compared to regular trials, as the latter entailed the prospect of an effortful task. Since the RewP, centroparietal Delta and Beta-gamma power were primarily related to monetary reward processing per se in previous EEG studies (i.e. in the absence of change in motivation; Bernat et al., 2015; Mas-Herrero et al., 2015; Webb et al., 2017; Weinberg and Shankman, 2017) we performed a systematic exploratory analysis on each of them. If confirmed, these results would therefore lend support to the assumption that these electrophysiological effects during feedback-based PM not only reflect reward processing (in conjunction with expectation), but also cost anticipation.

3. Methods

3.1. Participants.

Twenty seven undergraduate students from Ghent University (with normal or corrected-to-normal vision and no reported history of neurological or psychiatric disorders) freely participated in this experiment. Sample size was determined a priori based on an earlier EEG study that used a similar sample size and found clear cut amplitude modulations of FRN and FMT as a function of FB outcome and reward expectation with this same gambling task (Paul and Pourtois, 2017). They all gave written informed consent prior to the start of the experiment and were compensated about 30€ for their participation. This amount could be slightly lower (minimum 27.40€) depending on actual task performance (see below). The study was approved by the local ethics committee. One participant was excluded from further analyses due to the unexpected encounter of sickness during EEG recording. Hence, the total sample included 26 participants (21 females, age: M = 24.1 years, SD = 5.4).

3.2. Stimuli and task.

We used a gambling task that was previously validated (Hajcak et al., 2007). On each and every trial, participants had to choose one out of four doors by pressing with their right index finger the corresponding key on a response box. After a fixation dot (700 ms) this choice was followed by either positive FB (green “+”), indicating a win of 5 cents, or neutral no-reward FB (red “o”) (1000 ms). At the beginning of each trial, participants were informed about reward probability with a visual cue (600 ms), followed by a fixation dot (1500 ms). The cue was presented in the form of a small disk (pie chart) presented at fixation. Either one, two or three quarters were filled (black/white) corresponding to a reward probability of respectively 25, 50 or 75 %. Because four doors were presented for the

choice, a 25% reward probability therefore indicated that only one door actually contained the reward, two doors in the case of 50% reward probability and three doors for 75% reward probability. Unbeknown to participants, the outcome was actually only related to these probabilities (and not their actual choices), ending up with a preset winning of €12.40. Inter trial interval was fixed and set to 1000 ms. Hence, by crossing the three possible reward probabilities with the two opposite outcomes, six trial types were included in a factorial design. These six trial types were deemed "regular" and did not involve any specific effort or motivational component. Anticipated cost was low for them. To ensure participants paid attention to the cue and outcome, we also used catch trials randomly interspersed in the trial series (for a similar procedure, see Paul and Pourtois, 2017). Catch trials were identical to regular trials, except that a specific probe appeared either after the cue or FB. More specifically, in 24 trials at the cue offset this probe asked participants to report the winning chance ("How many doors contain a prize?", allowing responses from 1 to 3). In 24 different trials, they were asked about the expectedness of the outcome at FB offset, and answers were collected by means of a visual analog scale (VAS).

Besides regular trials, we also introduced "special" trials (i.e. they included a motivational component), where anticipated cost was transiently induced, selectively. Special trials only included 50% reward probability (maximum uncertainty) and were rewarded with 5 cents as well. Regular and special trials were shown in random order (for any reward probability and outcome condition). Special trials differed from regular trials by means of a specific visual cue lasting 1000ms and informing participants about the start of this "special" case. After this cue, trial structure of special trials was identical to regular trials, with the exception that the four doors were displayed in green color (as opposed to white color for regular trials) to remind participants of this special case throughout. After the choice, if the FB turned out to be a reward (50%),

then the trial terminated. However, if the FB turned out to be no-reward (50%), a second choice was submitted to the participants. They were invited to choose between two options: either to re-do this specific gamble or to carry on with a new gamble. If they decided to redo it, reward magnitude was increased to 10 cents. Hence, if they decided to redo it, they knew they might transform the no-reward just received – last gamble – to a possible rewarding outcome – new gamble within the same trial. We chose this specific reward magnitude to balance the maximum payoff between regular (5 cents/one gamble) and special trials (10 cents/two gambles). Nevertheless, because this gamble also had a 50% reward probability, reward uncertainty was still high. No time limit was imposed for this second choice. If they decided not to redo the gamble, then the trial terminated and they moved on to the next one. However and crucially, if they opted to redo the gamble, they were asked to complete another unrelated task first, namely a random dot clicking task (Klein et al., 2005; Sherdell et al., 2012; Treadway et al., 2009). This extra task therefore served as "stake" and involved an effort component. We devised this task to provide an ecological effort requirement that had both a physical and attentional part, as opposed to physical only (e.g. effortful gripping; Kurniawan et al., 2010; Pessiglione et al., 2007) or mental only (e.g. arithmetic calculation; Vassena et al., 2014). This random dot clicking task resembled the common bothering activity of closing pop-up windows while internet-browsing; it required a sustained activity (around 8 seconds) that participants deemed bearable most of the time, being driven by the prospect of an extra reward. Specific parameters defining the duration of the dot clicking task, as well as the probabilistic reward in redo-trials (10 cents), were selected after extensive pilot testing. These parameters allowed to set an optimal cost/benefit tradeoff (i.e. positive re-do choices > 50 %; see Results; pilot data are reported in Supplementary materials – Table 1). For special trials, we explicitly chose a 50% reward probability condition to provide a balanced amount of reward and no-reward trials,

which eased considerably data analyses and enabled us to avoid asymmetries in the signal-to-noise ratio between conditions.

This random dot clicking task was designed as follows: a small cross ("+", 1x1 mm) appeared at a random position on the screen until the participant clicked on it using the mouse, with 8 iterations of this task at 8 different locations (randomly selected at each iteration within a randomly generated list of 100 coordinates). Upon completion of the 8 successive clicks, a 500 ms screen announced the start of the redo-gamble, with the trial structure being identical to what is described above (see regular trials). Redoing the gamble resulted in either no reward (50%) or (10 cents) reward (50%). An additional amount varying between 0 and 2.60 € could be won with these special trials.

All stimuli were shown against a grey homogenous background on a 21-in CRT screen and controlled using E-Prime (V 2.0, Psychology Software Tools Inc., Sharpsburg, PA). At the end of the experiment participants were asked to rate the pleasantness and difficulty of the random dot clicking task using a continuous VAS, as well as their actual motivation to carry out it in order to redo the gamble. Additionally, they were asked to rate the pleasantness of the rewarding and no-rewarding FB, separately for regular (either 5 or 0 cent) and redo trials (following the clicking task - either 10 or 0 cent).

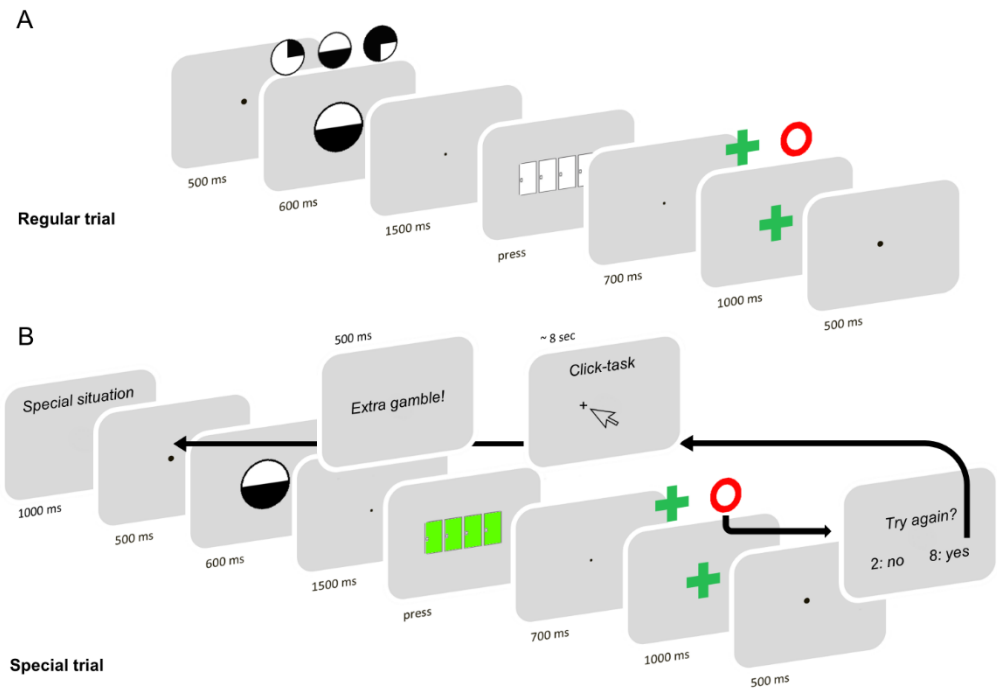


Figure 1. Overview of the task and trial structure. (A) In regular trials, participants were first informed about reward probability (by means of a black and white pie chart indicating 25, 50 or 75% winning probability, shown in random order). After they picked one door, they received either a reward (5 Euro cent) or no-reward FB, depicted by a green cross or red circle, respectively. (B) In special trials, at the beginning of the trial, a specific cue (i.e. the words “Special situation” written in Dutch) informed participants about the fact that these trials were special compared to the regular ones because reward probability was 50% only and, more importantly, in case of no-reward FB outcome they could choose to redo the gamble. During the door selection, the color of the doors was marked in green in order to remind them of this special case. If participants chose to redo the gamble after no-reward (which they did on a majority of trials; see results), an orthogonal dot clicking task (including effort expenditure) had first to be carried out before starting the gamble again. Reward magnitude was doubled for the second gamble in case of reward (i.e. 10 Euro cent) to maximize the probability of redoing the gamble after no-reward, as established based on pilot testing (see Supplementary materials).

3.3. Procedure.

After reading the instructions, participants were first familiarized with fourteen practice trials of the gambling task, including three special trials (two of them providing no-reward, thus allowing familiarization with the occurrence of a second choice now and then, and the random dot clicking task). In total, 392 trials were regular. One hundred and four trials were special. Given that special trials always involved a 50% reward probability, the choice to perform the random dot clicking task (and to redo the gamble) was eventually submitted 52 times to them in total. For FRN analyses, common practice suggests using at least 20 trials per condition (Marco-Pallares et al., 2011). With these considerations in mind, for the 25% reward probability condition, 144 trials were used, of which 108 with no-reward FB and 36 with reward FB. The reverse was obtained for the 75% reward probability condition. Last, for the 50% reward probability condition, 104 trials were used, half being rewarding (n=52) and the other half non-rewarding (n=52). The same trial type could be presented consecutively. The experiment consisted of four blocks comprising a random combination of 124 trials each. After each block, a short break was included and participants were informed about their current (cumulative) payoff.

3.4. Recording and Preprocessing of Electrophysiological Data.

EEG was recorded using a 64-channel Biosemi Active Two system (http://www.biosemi.com) with four additional electrodes measuring horizontal and vertical eye movements. EEG was sampled at 512 Hz and referenced to the Common Mode Sense (CMS) active electrode and Driven Right Leg (DRL) passive electrode. The EEG was preprocessed offline with EEGLAB 13.5.4b (Delorme and Makeig, 2004), implemented in Matlab R2012b. A 0.05/35 Hz high/low pass filter was applied after re-referencing the EEG signal to the averaged mastoids. An independent

component analysis was run on the continuous data. Individual epochs were extracted from -2000 to 2000 ms around FB onset and a pre-feedback baseline was subtracted (-250 to 0). Artefactual ICA components were manually selected focusing on eye artifacts and spatial or temporal discontinuities. A semi-automatic artefact correction procedure was applied to eliminate trials with voltage values exceeding ± 90 µV or slow voltage drifts with a stronger slope than ± 90 µV, as well as based on visual inspection. For each subject separately, artefact-free epochs were grouped according to the six regular and two special conditions. Regular trials included expected, no-expectations and unexpected[1] FB associated with reward (deriving from 75%, 50%, 25% reward probability trials respectively), and expected, no expectations and unexpected FB associated with no-reward (deriving from 25%, 50%, 75% reward probability trials respectively). Special trials involved only no-expectations FB, providing either reward or no-reward (from 50% reward probability special trials). To overcome getting different signal to noise ratios between conditions (Keil et al., 2014), the same number of trials (randomly sampled) was used for all of them, being defined subject-wise based on the condition with the lowest trial count.

The FRN was quantified at FCz as the difference between the most negative peak (N200: within 200 - 350 ms) and the average voltage of the preceding and following positive peaks (P170: within 150 - 250 ms, P300: within 250 - 600 ms), to control for possible confounding effects of the positive components surrounding the N200, as often performed in ERP studies (Chase et al., 2011; Oliveira et al., 2007; Sallet et al., 2013; Yeung and Sanfey, 2004). The RewP was defined as the average amplitude at Cz and FCz within the 235-285 ms interval post-feedback onset,

[1] These labels refer here to the objective reward probability and not the subjective expectation.

corresponding to the 50 ms window surrounding the peak of the difference reward – no-reward (Novak and Foti, 2015; see Fig. 3).

Time frequency analysis was done using EEGLAB built-in std_ersps() function, based on complex Morlet wavelet convolution (2 to 8.75 cycles, 0.8 to 35 Hz, 75 log spaced frequencies, 200 time points per epoch). The time interval -500 to -200 ms before FB onset was used for baseline normalization. FMT band power change (4 – 8 Hz) were defined as the mean within 200 – 400 ms, decibel (dB) converted (10*log10[power/baseline]) at FCz. The same approach was adopted for the estimation of Delta (0.8 – 3.9 Hz) and Beta-gamma (20 – 35 Hz) band power changes, defined respectively as the mean amplitude within 200 – 400 ms at a set of parietal sites (CPz, CP1, CP2, CP3, CP4) for Delta, and within 250 – 350 ms at a set of frontocentral sites (FCz, Fz, FC1, FC2) for Beta-gamma. Time windows[2] and channel locations were based on the band-specific maximal power from the grand average of all conditions in regular trials (Luck and Gaspelin, 2017; see Figs. 4-6).

3.5. Data Analysis.

For all analyses, significance alpha cutoff was 0.05. At the behavioral level, our main dependent variable was the number of redo (expressed in percentage) associated with special trials. For the catch trials at the cue level, the amount of correct responses was converted to percentage. At the FB level, the subjective ratings were first transformed to percentages, arbitrarily setting one anchor (‘very unexpected’) to 0 and the other one

[2] As visible from Figures 4 and 5 (panel B), the estimated power in the Theta and Delta bands peaked around 300ms following FB onset, demarcated by the 0 time point in these plots. Because the time/frequency convolution used assesses non-phase-locked event-related changes in the ongoing oscillatory activity, they can develop and peak rapidly after the time-locking event, even before a full period in a given frequency is actually completed (see also Cohen, 2014).

('very expected') to 100. These ratings were considered to be correct if the given value fell within a ± 20% range around the correct response (25, 50 or 75%. See Paul and Pourtois, 2017). Similarly, post-experiment VAS ratings of pleasantness of the FB (for regular and redo trials), as well VAS ratings of the random dot clicking task, were transformed to percentages setting anchors to the boundaries of the scales.

At the electrophysiological level, two sets of statistical analyses were performed. First, using the regular trials only, we assessed amplitude changes (FRN, RewP, FMT, Delta and Beta-gamma power) depending on reward probability and outcome. To this aim, repeated measures ANOVAs with FB expectation (expected, no expectations, unexpected) and outcome (reward vs. no-reward) as within-subject factors were performed. The trial count was equal across the six main conditions (regular trials): Msubject = 27.0, SDsubject = 4.0. Next, we compared FRN, RewP, FMT, Delta and Beta-gamma power for the no expectations condition only (i.e. 50% reward probability) between regular trials (no effort anticipation) and special trials (effort anticipation). To this aim, special trials that led to a no-reward and were eventually not redone by the participants (corresponding to a low number, see results below for actual proportion) were discarded from this analysis. Hence, with this second analysis, we could compare at the electrophysiological level the exact same outcome (either reward or no reward, with the same probability) when anticipated effort was absent vs. present (and eventually exerted). In this analysis, for each ERP component separately, a repeated measure ANOVA was carried out with trial type (special vs. regular) and outcome (reward vs. no-reward) as within-subject factors. The trial count was equal across the four main conditions (special vs. regular trials, with two outcome levels each time): Msubject = 36.3, SDsubject = 7.3.

Further exploratory Bayes Factor analyses (Rouder et al., 2017) were carried out with the JASP software package (JASP Team, 2017) with the default prior settings.

4. Results

4.1. Behavioral Results.

The accuracy for the cue (M correct= 84.5, SD = 11.5) and for the outcome (FB expectation: M correct = 69.5, SD = 18.4), as inferred from the catch trials, were well above chance level and compatible with a previous study where the same gambling task was used (Paul and Pourtois, 2017). Overall, for special trials, participants chose to redo the gamble most of the time (% yes: M = 79.8, SD = 30.97). However, five participants chose to re-do the gamble seldom (% yes: M = 21.9, SD = 11.7) and were deemed outliers (based on mean ± 1.5 standard deviations criterion). Accordingly, we excluded them from the subsequent analyses. On average, 1036 ms (SD = 853 ms) elapsed after no-reward FB before participants chose to redo the gamble (special trials). Post-experiment ratings confirmed that participants (n = 21 after removing the five outliers) reported to be motivated to carry out the random dot clicking task (M = 80.2 %, SD = 15.5)[3] in order to re-do the gamble. By comparison, a much lower motivation was observed for the five participants excluded (M = 42.3 %, SD = 35.2). Hence, there appeared to be a clear association between choosing to redo the gamble and be exposed to effort expenditure during the random dot clicking task, and its subjective evaluation in terms of motivation. Further, the ratings for the random dot clicking task showed that it was evaluated as being neutral and relatively easy (pleasantness: M = 48.5 %, SD = 29.7; difficulty: M = 20.0 %, SD = 20.1). Last, no significant differences were found between the evaluation of the reward FB after the regular (5 cent) and the redo trials (10 cent. t(20) = -1.139, p = .268, Cohen's dz = -0.25), nor between no-reward after the regular and the redo trials (t(20) = 1.254, p = .224, Cohen's dz = 0.27).

[3] Ratings of motivation and difficulty about the random dot clicking task were not reported by 3 participants. Related data refer to 18 out of 21 participants complying with exclusion criteria.

4.2. Electrophysiological Results.

In the first set of analyses, we assessed the effects of FB expectancy and FB outcome on each electrophysiological marker separately, using regular trials only. The analysis performed on the FRN amplitudes showed a significant main effect of expectation ($F(2, 50) = 8.55$, $p = .001$, $\eta^2p = .255$), outcome ($F(1, 25) = 16.38$, $p < .001$, $\eta^2p = .396$) and an interaction between these two factors ($F(2, 50) = 5.62$, $p = .006$, $\eta^2p = .184$), confirming its compatibility with the RPE framework (Fig. 2). The FRN component was larger for no-reward compared to reward FB (M reward = -9.42, SE = 0.72, M no-reward = -12.38, SE = 1.00) and unexpected compared to expected. Simple main effects of expectation were significant for no-reward ($F(2, 24) = 9.98$, $p = .001$, $\eta^2p = .454$), but not for reward FB ($F(2, 24) = 0.58$, $p = .569$).

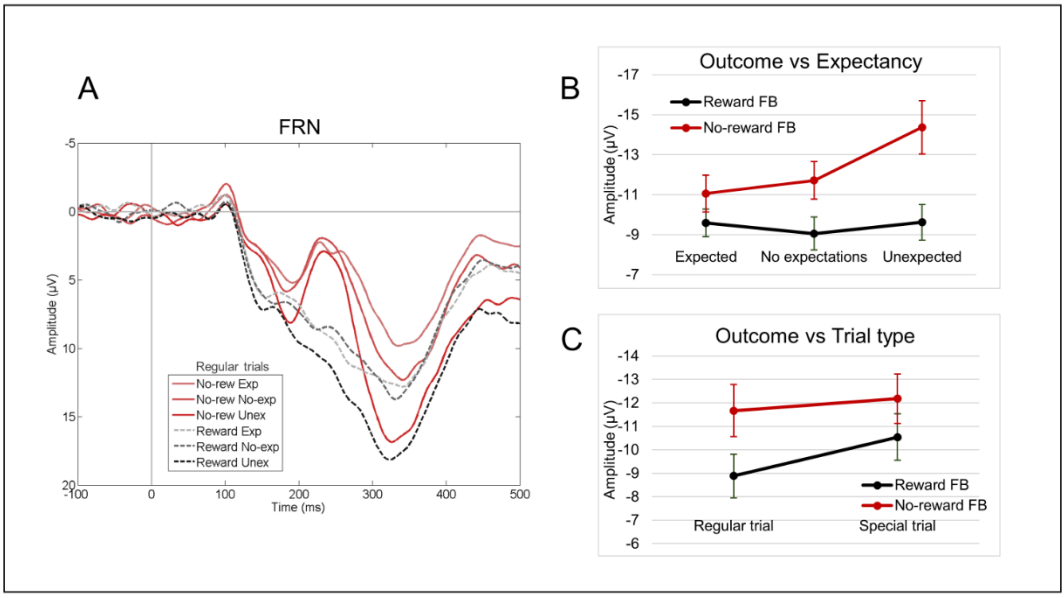


Figure 2. FRN results. (A) Grand average ERP waveforms computed at FCz for all six main conditions (regular trials). The FRN was computed as the difference between the most negative peak (N200: within 200 - 350 ms) and the average voltage of the preceding and following positive peaks (P170: within 150 - 250 ms, P300: within 250 - 600 ms). (B) A significant interaction between FB outcome and FB expectancy was evidenced for the FRN, whereby it was the largest for unexpected no-reward FB. (C) Mean amplitude of the FRN in the 50% reward probability condition as a function of effort anticipation (absent/regular trials vs. present/special trials) and FB outcome (reward vs. no-reward FB). The FRN was significantly larger for no-reward compared to reward FB, and for special compared to regular trials, but without interaction between these two factors. The error bar corresponds to 1 standard error of the mean.

The analysis performed on FMT power (Fig. 4) showed a significant main effect of expectation ($F(2, 50) = 16.06$, $p < .001$, $\eta^2p = .391$), and outcome ($F(1, 25) = 8.64$, $p = .007$, $\eta^2p = .257$), without a significant interaction between these two factors ($F(2, 50) = 0.31$, $p = .732$). The analysis performed on the RewP amplitudes (Fig. 3) showed a significant main effect of FB expectation ($F(2, 50) = 10.12$, $p < .001$, $\eta^2p = .288$) and outcome ($F(1, 25) = 57.22$, $p < .001$, $\eta^2p = .696$), without significant interaction between these two factors ($F(2, 50) = 1.04$, $p = .360$). The RewP was larger for reward compared to no-reward FB (M reward = 11.27, SE = 1.43, M no-reward = 5.06, SE = 1.35) and for unexpected compared to no-expectation and expected FB, with a significant decrease in amplitude with increasing expectation (linear contrast, $F(1,25) = 10.90$, $p = .003$, $\eta^2p = .304$).

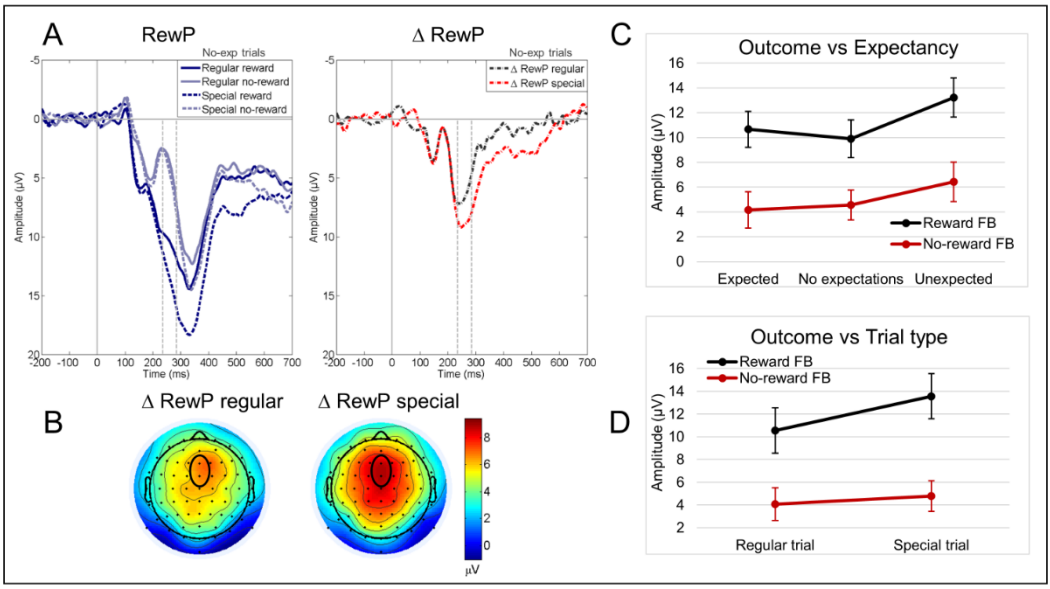


Figure 3. RewP results. (A) Grand average ERP waveforms from Cz and FCz pooled together for the 50% reward probability condition. The left inset shows the RewP for regular (solid lines) and special (dashed lines) trials, separately for reward (dark blue) and no-reward (light blue) outcome. The right inset shows the corresponding difference waves for the two main conditions (regular trials-black line and special trials-red line) obtained after the ERP activity for no-reward was subtracted from the one corresponding to reward. The RewP was computed as the average amplitude at Cz and FCz within the 235-285 ms interval post-feedback onset (the corresponding time-window for amplitude measurement and scoring is highlighted by the dashed vertical grey lines). (B) Horizontal topographies (top view) of the difference waves (reward minus no-reward), averaged from 235 to 285 ms, for regular (left) and special (right) trials. The black ellipse superimposed indicates FCz and Cz electrode locations. (C) Mean amplitude of the RewP for the six main conditions (regular trials), showing significant main effects of FB outcome and FB expectancy. (D) Mean amplitudes of the RewP in the 50% reward probability condition as a function of effort anticipation (absent/regular vs. present/special trials) and FB outcome (reward vs. no-reward FB). When the FB was rewarding, the RewP was larger for special compared to regular trials, without such modulation for no-reward FB, as indicated by a significant interaction between these two factors. The error bar corresponds to 1 standard error of the mean.

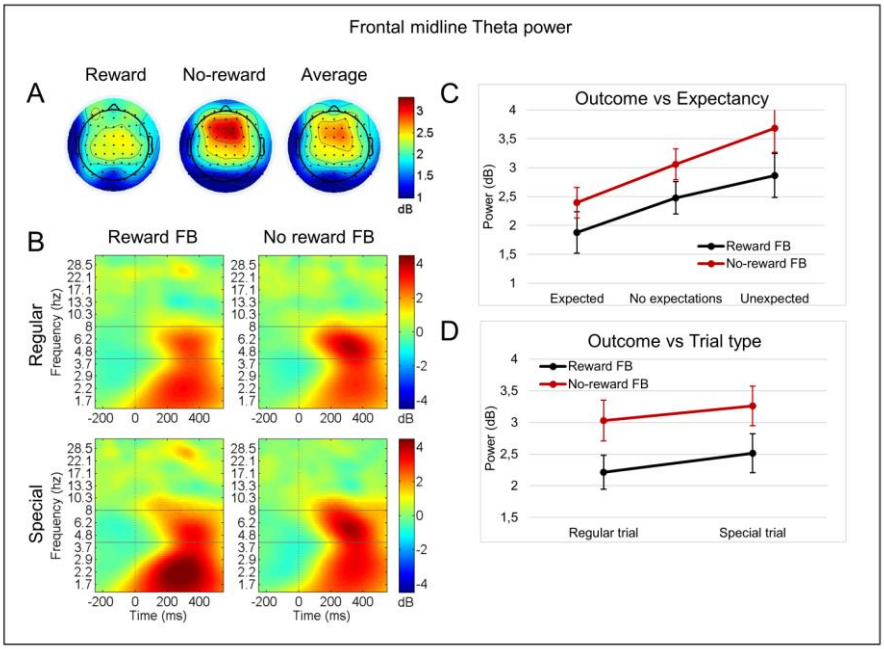


Figure 4. FMT results. (A) Horizontal topographies (top view) of the average FMT power change computed in the 200-400 ms window following FB onset (regular trials). When collapsing expectancy, a larger FMT power was seen for no-reward (center) than reward FB (left); (right) topography of FMT power for all conditions collapsed. (B) FMT (4-8 Hz) power changes from electrode FCz, comparing reward and no-reward FB for regular vs. special trials (50% probability condition). (C) Mean FMT power changes separately for the six main conditions (regular trials), showing significant main effects of FB expectancy and FB outcome. (D) Mean FMT power changes in the 50% reward probability condition as a function of effort anticipation and FB outcome. This analysis showed significant main effects of FB outcome and trial type, with larger FMT power values for no-reward than reward, and for special than regular trials. The error bar corresponds to 1 standard error of the mean.

Similarly to the RewP, the analysis performed on centroparietal Delta power (Fig. 5) showed a significant main effect of FB expectation ($F(2, 50) = 12.17$, $p < .001$, $\eta^2p = .327$), and outcome ($F(1, 25) = 20.75$, $p < .001$, $\eta^2p = .454$), without significant interaction between these two factors ($F(2, 50) = 3.09$, $p = .054$). Finally, the analysis performed on frontal Beta-gamma showed a trend for the main effect of FB outcome ($F(1, 25) = 3.57$, $p = .070$, $\eta^2p = .125$), with higher power values for reward ($M = 0.77$, $SE = 0.23$) compared to no-reward FB ($M = 0.42$, $SE = 0.14$). Notably, FB outcome had therefore opposite effects on these non-overlapping frequency bands, with higher FMT power for no-reward vs reward FB, but conversely higher Delta and Beta-gamma power for reward vs no-reward FB (see Figs. 4 and 5).

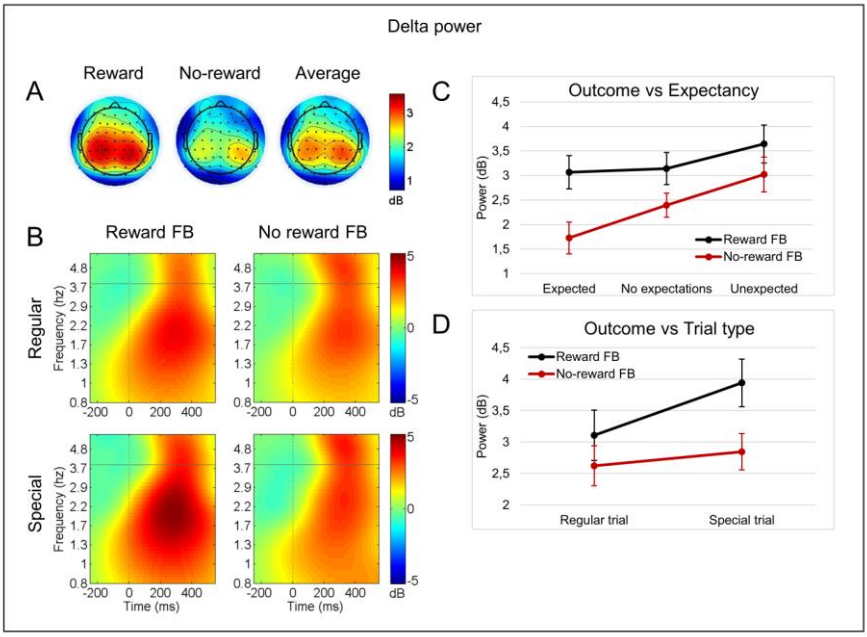


Figure 5. Delta results. (A) Horizontal topographies (top view) of the average Delta power change computed in the 200-400 ms window following FB onset (regular trials). When collapsing expectancy, a larger centro-parietal delta power was seen for reward FB (left) than no-reward FB (center); (right) delta power for all conditions collapsed. (B) Delta (0.8-3.9 Hz) power changes from centro-parietal electrodes (CPz, CP1, CP2, CP3, and CP4 collapsed), comparing reward to no-reward FB, for regular vs. special trials (50% probability condition). (C) Mean Delta power changes for the six main conditions (regular trials), showing significant main effects of FB expectancy and FB outcome, with larger values for unexpected than expected, and for reward than no-reward FB. (D) Mean Delta power changes in the 50% reward probability condition. Delta power was the largest when the FB was rewarding in special compared to regular trials, without such modulation for no-reward FB, as confirmed by a trend-significant interaction between these two factors. The error bar corresponds to 1 standard error of the mean.

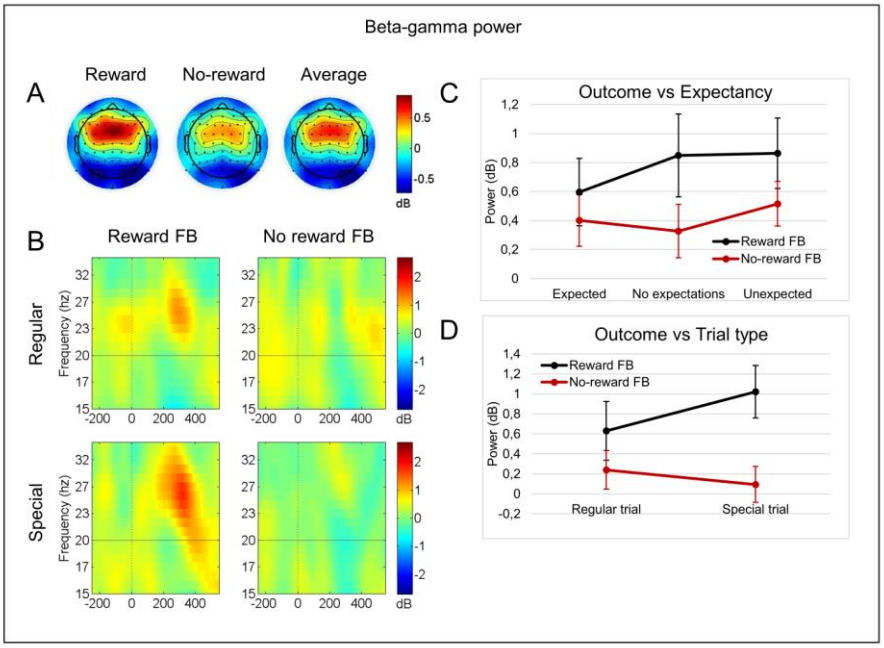


Figure 6. Beta-gamma results. (A) Horizontal topographies (top view) of the average Beta-gamma power change computed in the 250-350 ms window following FB onset (regular trials). When collapsing expectancy, beta-gamma power increased for reward FB (left) compared to no-reward FB (center); (right) beta-gamma power for all conditions together. (B) Beta-gamma (20-35 Hz) power changes from fronto-central electrodes (FCz, FC1, FC2, and Fz collapsed), comparing reward and no-reward FB, for regular vs. special trials (50% probability condition). (C) Mean Beta-gamma power changes for the six main conditions (regular trials), showing a t main effect of FB outcome only, translating larger power values for reward than no-reward FB. (D) Mean Beta-gamma power changes in the 50% reward probability condition. A significant interaction was found between the two factors showing larger power values for reward FB in special compared to regular trials. The error bar corresponds to 1 standard error of the mean.

In the second set of analyses, we assessed the effects of trial type and FB outcome, using special trials followed by a positive redo-choice and regular trials with the same reward probability - 50%. We first tested the hypothesis that the FRN amplitude might be lower for special no-reward (when the choice to redo was actually made, see methods and results above) compared to regular no-reward FB. This analysis showed a significant main effect of trial type ($F(1, 20) = 7.34$, $p = .013$, $\eta^2p = .269$) and FB outcome ($F(1, 20) = 8.76$, $p = .008$, $\eta^2p = .305$). The interaction between these two factors was not significant ($F(1, 20) = 1.50$, $p = .236$). The FRN was larger for no-reward compared to reward FB, and for special trials compared to regular trials. This latter difference was significant for reward ($F(1, 20) = 9.21$, $p = .007$, $\eta^2p = .315$. M regular = -8.88, SE = 0.94, M special = -10,54, SE = 0.99) but not for no-reward FB ($F(1, 20) = 0.55$, $p = .465$) (Fig. 2). Next, we tested the hypothesis that FMT power was larger for special no-reward (when effort was anticipated) compared to regular no-reward. This analysis showed a significant main effect of FB outcome only ($F(1, 20) = 16.15$, $p = .001$, $\eta^2p = .447$), with higher values for no-reward compared to reward FB. The main effect of trial type was not significant ($F(1, 20) = 1.69$, $p = .208$). No significant interaction between trial type and FB outcome was found ($F(1, 20) = 0.07$, $p = .795$) (Fig. 4). Hence, these two analyses failed to confirm the prediction that a second choice might influence (i.e. decrease) the processing of the negative valence of the FB (FRN and RPE), or that effort anticipation might increase cognitive control[4] (FMT power).

[4] We also explored possible changes occurring at the cue level between the two main conditions (see Supplementary Materials for numerical values and statistical results). Interestingly, FMT was larger for special than regular trials, likely suggesting some enhanced CC cue-based for the former compared to the latter ones. By comparison, the CNV component (ERP) was similar between these two conditions, suggesting that anticipation of the upcoming door selection task was balanced between them.

However, and interestingly, reward processing per se seemed to be influenced by the manipulation of effort anticipation, as suggested indirectly by the FRN data analysis reported above. To test this possibility, we analyzed the RewP ERP component using the same statistical model. This analysis showed a significant main effect of trial type ($F(1, 20) = 8.54$, $p = .008$, $\eta^2p = .299$) and FB outcome ($F(1, 20) = 55.89$, $p < .001$, $\eta^2p = .736$). The RewP was larger for reward compared to no-reward FB, and for special compared to regular trials. Importantly, this analysis also showed a significant interaction between trial type and FB outcome ($F(1, 20) = 6.82$, $p = .017$, $\eta^2p = .254$). As suggested indirectly by the FRN data analysis reported above, the RewP was significantly larger for special compared to regular trials when the FB was rewarding ($F(1, 20) = 9.54$, $p = .006$, $\eta^2p = .323$. M regular = 10.54, SE = 2.00, M special = 13.57, SE = 1.97) but not when it was not ($F(1, 20) = 1.92$, $p = .182$) (Fig. 3). Noteworthy, the analysis performed on centroparietal Delta power showed a similar effect, with a significant main effect of trial type ($F(1, 20) = 8.56$, $p = .008$, $\eta^2p = .300$), a significant main effect of FB outcome ($F(1, 20) = 12.43$, $p = .002$, $\eta^2p = .383$), and the interaction between FB outcome and trial type approaching significance ($F(1, 20) = 4.14$, $p = .055$, $\eta^2p = .171$). Delta power values were larger for reward compared to no-reward FB, and for special compared to regular trials, with this latter difference being significant for reward ($F(1, 20) = 13.10$, $p = .002$, $\eta^2p = .396$), but not for no-reward FB ($F(1, 20) = 0.89$, $p = .358$) (Fig. 5). Finally, the analysis performed on frontal Beta-gamma power showed a significant main effect of FB outcome ($F(1, 20) = 6.57$, $p = .019$, $\eta^2p = .247$) and importantly, a significant interaction between trial type and FB outcome ($F(1, 20) = 4.80$, $p = .040$, $\eta^2p = .194$). Beta-gamma oscillations increased for reward compared to no-reward FB. Interestingly, this latter difference was significant for special trials ($F(1, 20) = 12.22$, $p = .002$, $\eta^2p = .379$. M reward = 1.02, SE = 0.26, M no-reward = 0.10, SE = 0.18) but not for regular ones

($F(1, 20) = 1.67$, $p = .212$. M reward = 0.63, SE = 0.29, M no-reward = 0.24, SE = 0.19) (Fig. 6).

As suggested by the RewP and beta-gamma results reported above (as well as Delta to a lesser degree), reward processing was increased when effort expenditure could be avoided. Accordingly, it is conceivable that the five subjects who chose the re-do the gamble seldom (and were excluded from the analyses) might show an equal or even stronger gain in reward processing when effort could be avoided since their behavior translated effort avoidance. To test this assumption indirectly, we performed auxiliary Bayesian factor analyses using the full sample (n=26 participants). For each electrophysiological marker of reward processing separately (RewP ERP component, Delta and Beta-gamma power), we tested by means of a Bayesian paired samples t-test the strength of the evidence in favor of the alternative hypothesis that posited a larger amplitude value for reward processing in special (where effort anticipation was induced) compared to regular trials (where it was absent). Results showed that the alternative hypothesis was 39.5, 41.8, and 1.4 times more likely than the null for RewP, Delta and Beta-gamma power, respectively. These results provide thus very strong evidence in favor of an increase in reward processing at the RewP and Delta power levels when effort could be avoided.

Finally we explored, across the whole sample (n = 26), if the percentage of redo correlated with these electrophysiological effects. For each electrophysiological marker of reward processing separately, we first computed a difference-score by subtracting the mean activity for the regular from the special trials. Non-parametric correlations by means of Spearman's Rho were used. However, these correlations failed to reveal significant effects (RewP: $rs = -0.105$, $p = 0.611$; Delta: $rs = 0.247$, $p = 0.225$; Beta-gamma: $rs = 0.319$, $p = 0.112$). To note, the percentage of redo was high for the whole sample, with 11 participants that redid the

gamble 100% of the time, hence the inter-individual variability was low for this metric.

5. Discussion

To explore modulatory effects of cost anticipation on PM and reward processing, we used a previously validated gambling task in combination with a random dot clicking task (deriving from the work of Sherdell et al., 2012; and Treadway et al., 2009). To this end, two trial types, shown in random order, were used and compared: regular trials that did not involve cost anticipation, and special ones where a random dot clicking task could be carried out in case of no-reward as outcome, with the hope for the participants to transform this worse than expected event into a rewarding one. As a result, cost anticipation was increased in the latter compared to former trials, while all other dimensions were kept similar. A number of important new results emerge from this study. Cost anticipation reliably influenced the RewP and Delta (as well as Beta-gamma) power, but not the FRN and FMT, suggesting a direct influence on reward processing (as opposed to RPE signals captured by the FRN, or the need for CC, as reflected by FMT). More specifically, using these well-established neurophysiological markers of reward processing (RewP, Delta and Beta-gamma power), we found evidence for each of them for a systematic enhancement of this reward-based processing at the FB level when cost anticipation was activated, but the choice and ensuing dot clicking task could eventually be avoided. The uncertain outcome of the first gamble turned out to be rewarding, precluding in turn to perform a second choice and importantly, cancelling the second choice and random dot clicking task.

Our first set of analyses (regular trials) confirmed that FRN was sensitive to RPE (Holroyd and Coles, 2002; Walsh and Anderson, 2012), which was a pre-requisite to assess subsequently effects of cost anticipation on it, in special trials. Unexpected no-reward FB yielded the largest FRN, as dominant models of PM would predict (Ullsperger et al., 2014a, 2014b). Further, no-reward and unexpected FB led to substantial

FMT power increases compared to rewarding and expected FB, replicating previous EEG findings obtained with the same gambling task (Hajcak et al., 2007; Paul and Pourtois, 2017; see also Sallet et al., 2013). Although FRN and FMT power showed similar effects during reward processing at the FB level, yet these two markers did not fully overlap, and hence they might reflect different processes. Unlike the FRN, FMT power did not show a significant interaction between outcome and reward expectation, which is consistent with the assumption that spectral perturbations in this specific frequency band over medial frontal areas reflect signed RPEs only indirectly, especially when the evoked and induced activities are not disentangled from one another (Hajihosseini and Holroyd, 2013). Presumably, the total FMT power captures expectation's violation, conflict detection and/or the need for CC, rather than RPE per se or exclusively (Cavanagh et al., 2012; Cavanagh and Frank, 2014; Cohen and Donner, 2013). Interestingly, RewP, Delta and Beta-gamma power had opposing valence effects and non-overlapping scalp distributions compared to the FRN and FMT, showing larger amplitudes at central, centro-parietal and fronto-central electrodes for reward than no reward FB. RewP and Delta also showed increases in signal strength with increasing (reward) uncertainty, while Beta-gamma did not.

At the behavioral level, we found that the parameters chosen (see supplementary materials section for details) eventually created an optimal tradeoff between effort exertion (i.e. random dot clicking task) and the extra reward prospect to allow us to explore reward processing at the EEG level when cost anticipation was elicited: for special trials, the majority of participants (i.e., 21 out of 26 included in the sample) eventually chose to redo the gamble most of the time upon the experience of an unexpected no-reward outcome in these special trials, hence they decided to perform the auxiliary random dot clicking task and thereby exerted efforts, translating (enhanced) incentive motivation (Berridge and Robinson, 2003, 1998). Notwithstanding the presence of cost and effort anticipation

in these trials, at the EEG level, we failed to observe an increase of FMT power, however. Similarly, despite the overall preference toward the opportunity to undo the loss, we failed to observe a decrease of FRN amplitude in the same condition. Nonetheless, when considering direct electrophysiological markers of reward processing (as opposed to RPE for FRN, or the need for CC in the case of FMT power), namely RewP, centroparietal Delta and frontocentral Beta-gamma power, we found that cost anticipation did reliably modulate their amplitudes, suggesting the timely integration of reward and effort/cost anticipation during evaluative FB processing. While this interaction effect was at trend level only for the Delta power, it was clearly found when considering the RewP ERP component and Beta-gamma power changes: these markers were substantially increased for rewarding FB when comparing special to regular trials, hence when comparing trials with vs. without cost anticipation. In other words, participants appeared to assign more hedonic or positive value to the rewarding FB when it signaled that extra effort expenditure was precluded (special trials), compared to a control condition where anticipated effort was always absent/omitted (regular trials), corroborating the assumption that cost anticipation and reward signals were timely integrated at this level. Because reward expectation was intermediate (50%) and balanced between these two conditions, this variable cannot account for this effect. Likewise, reward magnitude was matched between them, ruling out the possibility that this factor could explain this modulatory effect. Moreover, an auxiliary data analysis based on Bayes factors and run on the full sample (n=26) confirmed strong evidence in favor of a significant increase in the amplitude of the RewP ERP component as well as Delta power when reward processing was accompanied by the avoidance of this anticipated cost.

Although the modulation of reward-related effects on FB processing was mainly related to an anticipatory component during special trials, the trial structure did not allow us to parse effort anticipation per se, from a

more general cost associated with the consequences of the subsequent choice (i.e. to redo the gamble most of the time). At the time of FB delivery after the first gamble (special trials), participants likely anticipated and integrated not only the need to execute an effortful task, but also the time they would therefore need to spend on it and the second gamble ensuing. Accordingly, the enhanced reward-related activity seen for the first gamble during special trials in case of reward outcome might result from the blend of multiple processes and components. As surmised above, opportunity cost (Kurzban et al., 2013) is thought to play an important role in this modulation. In the present case (cf. special trials), a cost arose and was likely computed and rapidly integrated with reward because participants anticipated they had to spend some time doing another task (i.e. the dot clicking task) and thus consume mental resources for it, something that precluded their allocation to another valuable task or activity (the gamble). Further, not only did the effortful dot clicking task impeded or interfered now and then with the main task (gambling), it probably also artificially prolonged the total time they had to spend before they could eventually complete the experiment and leave the laboratory. Hence, it appears parsimonious to assume an interaction effect between reward and a more general cost anticipation to explain these results. This general cost likely corresponded to the effort itself as well as the associated opportunity cost. Moreover, given that the analyses performed on reward-related EEG markers were exploratory in nature, we sought to corroborate this conclusion more directly and firmly at the empirical level. To this aim, we ran a control behavioral experiment (see supplementary materials for details) where we used a similar experimental procedure and task (without EEG and including less conditions), but critically, we added now and then subjective ratings of the FB along specific affective dimensions during task execution. Confirming our interpretation, results of this control behavioral experiment showed that reward FB encountered during special trials was associated with higher levels pleasantness and relief (without changes in

frustration however) compared to the same reward FB encountered during regular trials (see Fig. 1 – Supplementary Materials). Combined together, these new results therefore lend support to the assumption that reward and cost anticipation are timely integrated during FB processing. Moreover, they suggest that standard electrophysiological markers of reward processing in humans (namely the RewP ERP component and frontocentral Beta-gamma power changes) track changes in motivation to some extent, and more specifically incentive motivation (assuming that motivation to engage in rewarding tasks or activities critically depends on perceived effort). As such, they are broadly consistent with the ubiquitous principle of economy that rules many facets of human decision making (Botvinick and Braver, 2015; Hull, 1943; Westbrook and Braver, 2016), whereby when effort to gain rewards can be avoided (because of a specific choice made or task configuration/set), reward processing is in turn transiently enhanced.

Our new findings also have important methodological and clinical implications. For example, Anhedonia is usually viewed as a cardinal diagnostic and endophenotypic feature of several emotional disorders, including MDD (Pizzagalli, 2014). Moreover, recently MDD has been associated with blunted RewP and/or posterior parietal Delta power in different EEG studies, suggesting decrease reward processing during gambling in these patients relative to healthy controls (Olbrich and Arns, 2013; Proudfit et al., 2015; Webb et al., 2017; Weinberg and Shankman, 2017; Whitton et al., 2016). As our new EEG results indirectly suggest, amplitude variations of the RewP and posterior parietal Delta can be observed (in healthy controls) when reward expectation is kept constant, but cost anticipation varies systematically across conditions, with effort avoidance clearly increasing reward processing. Intriguingly, a decreased RewP and/or posterior parietal Delta power in MDD might in principle reflect an abnormal integration of reward with cost anticipation, as opposed to decreased reward processing per se. Additional EEG studies

are therefore needed to assess the actual contribution of cost anticipation vs. reward (and their joint effect) to amplitude modulations of these electrophysiological markers of reward processing in MDD during gambling and PM.

Some limitations warrant comments. Presumably, the lack of systematic amplitude modulation of the FRN as a function of the opportunity to undo a loss, as was initially hypothesized, might be partially related to the specifics of our experimental procedure. Because we used monetary reward as main incentive, defensive motivation or negative affect was probably not elicited in case of no-reward outcome. This might account for the lack of systematic amplitude modulation of the FRN or FMT as a function of cost or effort anticipation in the present case. Moreover, although our new results are compatible with the HRL-ACC theory (Holroyd and Umemoto, 2016), here we used a gambling task devoid of learning, a factor which may have reduced artificially the need for CC in case worse than expected outcome was experienced, accounting in turn for the lack of systematic amplitude variations of the FRN and FMT with the elected cost anticipation manipulation. However, the lack of learning was an advantage because we could easily compare at the EEG level special to regular trials without considering specific bins or time intervals. Last, we acknowledge that it would probably have been better to compare two conditions that only differed in terms of effort, being either low or high for example (Vassena et al., 2014). However, we had to include additional conditions in the design in the present case (see regular trials) to ascertain first that the electrophysiological markers under scrutiny were sensitive to feedback expectancy and valence, as previously found. Adding them eventually made the design more complex. However, it was an important pre-requisite at the methodological level. Accordingly, future studies where a more controlled parametrization of cost is achieved are needed to better disentangle which underlying component of cost is causally related to the changes observed in reward processing at the FB level. In

this context, the results reported in this study ought to be seen as a first attempt to explore systematically the malleability of standard electrophysiological markers of PM to changes in reward and cost anticipation concurrently.

To conclude, the results of this study show that reward and cost anticipation integrate with one another during FB processing after gambling. Reward processing, as measured using RewP amplitude and frontocentral Beta-gamma power (as well as posterior parietal Delta power), was increased when extra effort could occasionally be avoided, in line with the broad principle of economy and the aversiveness of effort anticipation. Moreover, at the subjective level, participants evaluated this FB as more pleasant (and relieving) compared to the same FB provided without any cost component. All in all, these results dovetail with the assumption that incentive motivation (where effort and reward are considered concurrently) dynamically shapes FB processing during gambling. As such, these new results might have implications for identifying stable or reliable electrophysiological markers of Anhedonia, which is usually characterized by both reward-related and motivational impairments (Sherdell et al., 2012; Treadway et al., 2012). Ultimately, systematically exploring changes in reward processing depending on cost anticipation at the ERP and time-frequency levels in MDD patients, as done here in healthy adult participants, could help better disentangle if the observed impairments during FB based reward processing actually stems from abnormal reward processing per se, or instead a complex interaction effect between reward and cost anticipation.

6. Supplementary Material

6.1. Methods.

6.1.1. Participants.

Sixteen students (14 females), recruited with the same criteria and from the same student population as the main EEG study, participated in this follow-up behavioral experiment. They were compensated with a variable 10.20-12.80€ amount for their participation.

6.1.2. Task.

A modified version of the gambling task was devised. Trials with 25% or 75% reward probability were not included. Hence, the cue always corresponded to a 50% reward probability (i.e. pie chart half filled). Catch trials for the cue were therefore omitted because reward probability was constant throughout the experiment. Since we wanted to assess emotional feelings for the FB outcome (and compare special with regular trials), we added multiple ratings following the FB. These ratings probed the pleasantness, frustration and relief experienced following the FB, and were reported using specific visual analog scales (VAS). These three ratings were submitted each 48 times in total, 1000ms after the offset of the FB. For each condition (regular vs. special trials) and outcome (reward vs. no reward), they were presented 12 times in total.

6.1.3. Procedure.

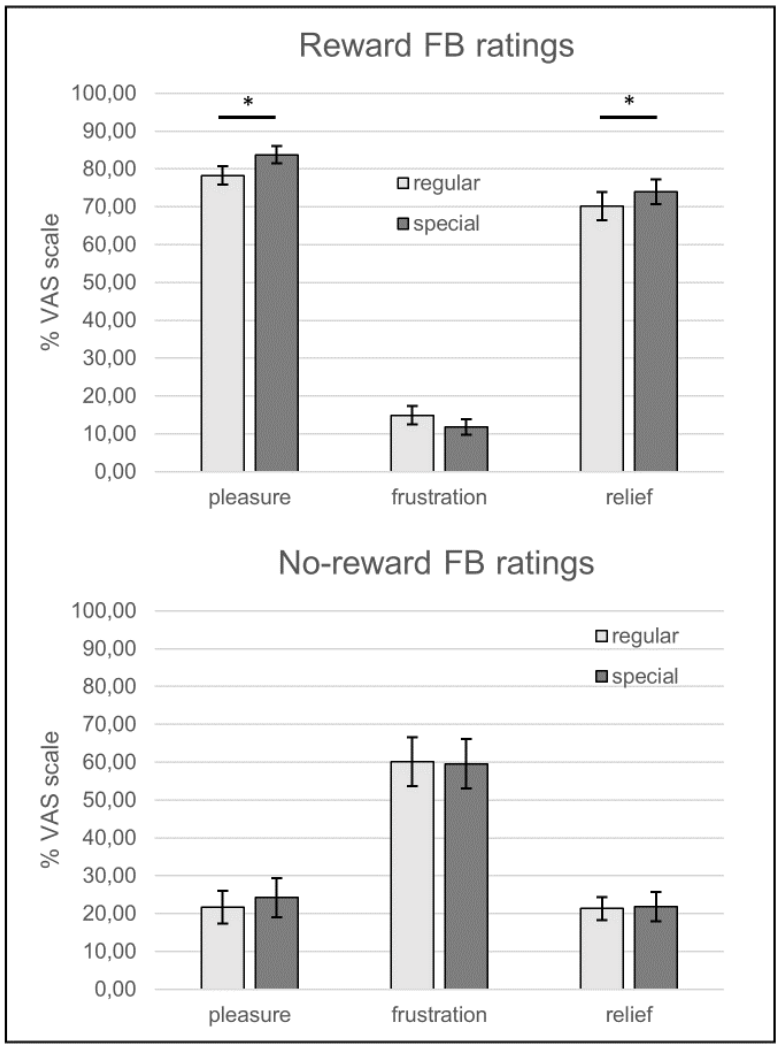
The same procedure as in the main EEG experiment was used here, with the following changes. We used four blocks, each composed of 52 trials. In total, 104 regular and 104 special trials were presented in random order across these four blocks.

6.1.4. Data analysis.

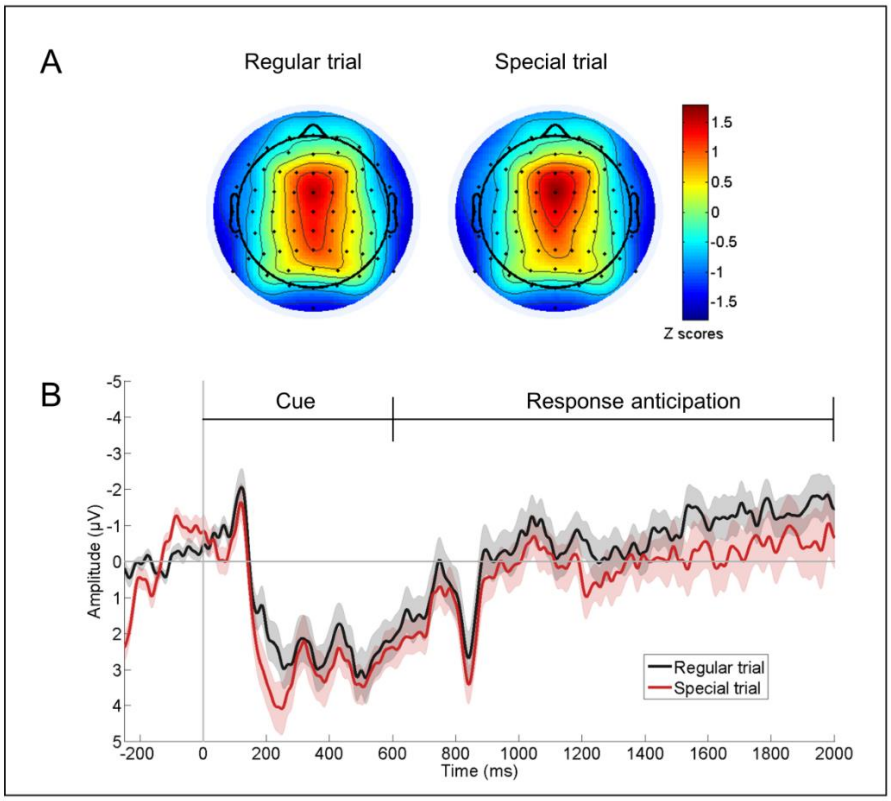
The VAS scores for each condition (regular vs. special trials), FB outcome (reward vs. no reward), and affective dimension (pleasantness, frustration or relief) were averaged across the 12 presentations and across subjects. These values were then transformed to percentages setting anchors to the boundaries of the scales. One-tailed paired t-tests were run for the FB ratings probing “pleasure” and “relief”, testing for higher values from reward FB in special vs. regular trials. Conversely, a one-tailed paired t-test was run for the FB rating probing “frustration”, testing for higher values from no-reward FB in special vs. regular trials. For all analyses, significance alpha cutoff was 0.05.

6.2. Results.

Participants reported more pleasantness for the reward FB in special ($M = 83.75$, $SE = 2.31$) compared to regular trials ($M = 78.27$, $SE = 2.48$), $t(15) = 2.71$, $p = .008$, $d = 0.57$. They also reported more relief for this FB in special ($M = 74.01$, $SE = 3.28$) compared to regular trials ($M = 70.17$, $SE = 3.71$), $t(15) = 1.98$, $p = .033$, $d = 0.27$. By comparison, no significant difference in levels of frustration was found between the two trial types for no-reward FB ($t(15) = - 0.19$, $p = .427$). (Supplementary Figure 1).



Supplementary Figure 1. Results of control behavioral experiment. Participants rated now and then, using a visual analog scale (VAS), FB (reward vs. no-reward) along three dimensions (pleasure, frustration and relief), separately for regular and special trials. Pleasure and relief were larger for reward than no-reward FB. Conversely, frustration was larger for no-reward than reward. Interestingly, when comparing special to regular trials, we found that participants reported significantly more pleasure and relief for reward FB for the former compared to the latter condition, consistent with a gain in reward processing when effort could be avoided. By comparison, no difference in negative feelings (frustration) or positive ones was found for no-reward FB between the two main conditions.



Supplementary Figure 2. Results of cue-locked analyses. (A) Horizontal topographies of the average FMT power during the cue presentation (600ms) separately for regular and special trials. In the pre-cue interval, these two conditions were not properly matched because a previous additional cue, informing about the onset of a special case, was displayed for special trials only. This additional event in special trials created a burst in the Theta activity that lasted until the pre-cue interval. To overcome this problem, we extracted the FMT power along the whole cue epoch by means of Fast Fourier Transform and applied a topographical normalization. FMT power at each site was divided by the summed FMT power across all sites, and a within-subject Z-score was then obtained by normalizing over all electrodes. A paired samples T-test performed on normalized Theta power, extracted from channel FCz, showed an increased FMT activity for special compared to regular trials [$t(25) = 2.863$, $p = 0.008$, $d = 0.562$]. (B) Grand average ERP waveforms (channel Cz) time-locked to the cue, separately for regular and special trials. The shadowing indicates one standard error of the mean. The CNV (contingent negativity variation) was defined as the mean ERP activity at electrode Cz extracted during the 1000-2000ms interval following cue onset, relative to a 250ms pre-cue baseline interval. Its amplitude was similar between these two conditions [$t(25) = 1.012$, $p = 0.321$].

Data from the six pilot participants

pilot	clicks	reward	% yes
1	5	10	96
2	8	10	63
3	20	10	0
4	10	5	7
5	8	10	90
6	8	10	17

Table 1. Data from the six individual pilot participants (none of them participated to the main EEG experiment or control behavioral experiment) tested prior to the EEG experiment to specify the optimal number of clicks to be used (8) for the random dot clicking task, as well as reward magnitude for the following (redo) gamble (10 eurocent) (special trials). In these conditions (8 clicks and 10 eurocent), we found that participants were inclined to redo the gamble most of the time, which was an important pre-requisite for our EEG data analysis and the comparison of reward processing at the FB level (following the first gamble) when effort anticipation was absent vs. present (and later exerted).

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Chapter 4: The rewarding effects of cognitive effort avoidance and exertion[1]

[1] Gheza, D., Vassena, E., Baeken, C., De Raedt, R., & Pourtois, G. (submitted). The rewarding effects of cognitive effort avoidance and exertion: an electrophysiological investigation

1. Abstract

During choice behavior, humans try to maximize potential benefits while minimizing costs. Generally, this translates into avoidance of behaviors requiring mental or physical effort. In a previous study, we showed that avoiding cost (i.e., to perform an additional task) could enhance reward processing. This “relief” effect was associated with increased amplitude of the Reward Positivity (RewP) event-related (ERP) component (Gheza, De Raedt, Baeken, & Pourtois, 2018). In the current study, we sought to extend these findings by investigating whether the rewarding effect of effort avoidance is modulated by the amount of cognitive effort anticipated. Participants performed a gambling task where effort anticipation (high vs. low) and gambling outcome (monetary reward vs. no-reward) were manipulated on a trial by trial basis while 64-channel electroencephalogram (EEG) was recorded. Participants knew that upon no-reward outcome they would need to perform an orthogonal effort task. Prior to the gamble, a cue indicated whether such effort task would be easy or hard. In case of reward outcome, no task followed. Critically, this manipulation allowed us to compare reward processing when avoiding a hard as compared to an easy task. We extracted and compared electrophysiological markers associated with reward processing (RewP, Delta and Beta-gamma power) and time-locked to the gambling feedback (FB), as well as the RewP after the subsequent effort task. Results showed that the RewP was larger for the FB when a hard compared to easy task was anticipated, however, irrespective of the outcome of the gambling. No such effect was observed for Delta or Beta-gamma power. In comparison, after the effort task, the RewP was larger for reward following the hard compared to easy task. These results suggest that reward processing is not necessarily increased when high as compared to low effort can be avoided, while it is clearly enhanced after the successful completion of an effortful task.

2. Introduction

The prospect of reward drives a wide range of human behaviors, and is key for reinforcement learning and decision-making. Reward is a potent motivational drive that helps individuals to maximize their fitness (Berridge & Kringelbach, 2015). An influential theory proposed that reward processing subsumes different components, processed by partially dissociable neural circuits (Berridge & Robinson, 2003): learning, liking, and wanting. In this framework, 'wanting' refers to incentive salience whereby a given stimulus becomes, either through learning or because of specific intrinsic properties, desired and wanted, and effort is expended to approach or reach it. 'Wanting' is supported by a distributed neural network, including mesolimbic dopamine (DA) projections, and DA interaction with glutamate (Berridge, Robinson, & Aldridge, 2009). By promoting approach toward rewards, 'wanting' has strong ties with effort expenditure. The involvement of the DA system in the willingness to exert effort in exchange for rewards has been corroborated by animal studies (Salamone, Correa, Farrar, & Mingote, 2007; Salamone, Cousins, & Bucher, 1994). Alteration of these mechanisms could account for impaired motivation in major depression or schizophrenia (Dunlop & Nemeroff, 2007; Treadway & Zald, 2011), where a hallmark is the so-called "decisional anhedonia", i.e. abnormal reward-based decision making (Barch, Pagliaccio, & Luking, 2016; Culbreth, Moran, & Barch, 2018; Treadway, Bossaller, Shelton, & Zald, 2012; Treadway & Zald, 2011).

Although these accounts assume that effort and reward processing are intertwined and underlie cost/benefit computations, the exact mechanism by which effort and reward integration occurs remains unclear, especially from a neurophysiological perspective. However, this assumption is backed up by the observation that physical or cognitive effort exertion can devalue rewards, a phenomenon called "effort discounting" (Apps, Grima, Manohar, & Husain, 2015; Botvinick,

Huffstetler, & McGuire, 2009; Croxson, Walton, O'Reilly, Behrens, & Rushworth, 2009; Westbrook, Kester, & Braver, 2013). Neuroimaging studies showed that the ventral striatum and/or the dorsal anterior cingulate cortex (dACC) likely process this integration of effort with reward information. This integration can be performed prospectively, regarding the net value of an upcoming action (Croxson et al., 2009), during effort-based decision-making (Chong et al., 2017; Prevost, Pessiglione, Metereau, Clery-Melin, & Dreher, 2010), as well as retrospectively, discounting reward based on previous mental-effort demands (Botvinick et al., 2009). Moreover, the anticipation of an upcoming effortful task elicits increased activity in brain regions typically associated with reward processing, including striatum and dACC, suggesting that these brain regions might be involved in enhancing task engagement or preparation induced by the prospect of both greater benefit and effort (Vassena et al., 2014). Notably, the electrophysiological effects of reward and (attentional) task demands can be temporally dissociated during task anticipation, but they may be integrated during performance monitoring (Schevernels, Krebs, Santens, Woldorff, & Boehler, 2014).

This line of empirical evidence was formalized in several neurocognitive models of motivation and decision-making. Shenhav and colleagues (Shenhav, Botvinick, & Cohen, 2013) proposed that cognitive control requirements are traded off against potential reward, and that the resulting signal reflects how valuable exerting control can be (as in performing an effortful task in exchange for reward). The dACC may be the neural substrate implementing this mechanism, as proposed by a recent computational account (Silvetti, Vassena, Abrahamse, & Verguts, 2018; Verguts, Vassena, & Silvetti, 2015). In this framework, adaptive allocation of effort is learned through reinforcement learning, implemented by the bidirectional interaction of midbrain reward signals and dACC cost-benefit trade-off signals. An alternative account suggests that dACC monitors and predicts the occurrence of salient events (Alexander &

Brown, 2011), and particularly motivationally salient events (Vassena, Deraeve, & Alexander, 2017). In this view, predictions about reward and effort, and prediction errors (mismatches between expected and actual reward and effort), drive learning and decision-making, and motivational impairments may derive from abnormal effort and reward prediction (Vassena et al., 2017). In comparison, the hierarchical RL theory – HRL-ACC (Holroyd & McClure, 2015; Holroyd & Umemoto, 2016; Holroyd & Yeung, 2012) proposed that the ultimate function of the dACC is learning the value of a task, and utilizing reward information to select task execution and leverage cognitive control allocation (i.e., ACC is seen primarily as a task selector).

At the scalp electroencephalographic (EEG) level, several event-related brain potentials (ERPs) have been identified in the past during performance monitoring, and closely related to the activity of the medial prefrontal cortex, comprising the dACC. They include the error related negativity (ERN) and the Reward Positivity (RewP, related to the feedback related negativity – FRN – in earlier ERP work), being time-locked either to response onset or feedback (FB) presentation during either reinforcement learning (RL) or gambling tasks (Holroyd & Coles, 2002; Holroyd, Pakzad-Vaezi, & Krigolson, 2008; Proudfit, 2015; Ullsperger, Fischer, Nigbur, & Endrass, 2014). Moreover, in the time-frequency domain, frontal midline theta (FMT) oscillations have been put forward as a valid marker of cognitive control, usually increasing for response errors or negative (no-reward) FB (Cavanagh, Frank, Klein, & Allen, 2010; Cohen, Wilmes, & van de Vijver, 2011; Gheza, De Raedt, et al., 2018). The RewP is a positive ERP component, peaking at fronto-central channels around 250 ms after evaluative FB onset. This component is typically larger for reward compared to no-reward outcome (Proudfit, 2015), and integrates outcome value and expectation (Eppinger, Kray, Mock, & Mecklinger, 2008; Gheza, Paul, & Pourtois, 2018; Sambrook & Goslin, 2015). Moreover, the RewP's amplitude is thought to reflect

individual reward sensitivity (Proudfit, 2015; Weinberg & Shankman, 2017), and is likely modulated by signed reward prediction error (RPE) signals, generated in dopaminergic neurons of the midbrain and conveyed to the ACC, which may use them to adjust subsequent behavior according to RL principles (Holroyd & Coles, 2002; Walsh & Anderson, 2012). On the other hand, in the time-frequency domain, FMT power increases for a quite diverse range of phenomena, including novel events or stimuli, response errors (Cavanagh, Cohen, & Allen, 2009), response conflict (Cohen & Donner, 2013), as well as evaluative FB used to trigger behavioral adaptation and learning (Cavanagh et al., 2010; Gheza, Bakic, Baeken, De Raedt, & Pourtois, 2019; van de Vijver, Ridderinkhof, & Cohen, 2011). With regards to FB processing, phasic bursts of FMT activity are usually elicited between 200 and 400 ms after FB onset as a function of both FB valence (larger for negative than positive) and FB expectancy (larger for unexpected than expected), but not their interaction, thus being compatible with unsigned prediction errors (PE) (Cavanagh, Figueroa, Cohen, & Frank, 2012; Gheza, De Raedt, et al., 2018). Moreover, FMT power increases along with cognitive demands and effort (Mussel, Ulrich, Allen, Osinsky, & Hewig, 2016), and a recent study showed that fluctuations in trial-by-trial FMT power during cued task switching predicted the efficacy of cognitive control, reflected in reduced switch cost (Cooper et al., 2019). Given these striking electrophysiological properties, it has been proposed that phasic bursts in FMT activity convey the need for enhanced cognitive control upon the encounter of challenges or surprising events, by binding or entraining distributed neural systems involved in their resolution (Cavanagh & Frank, 2014). Similarly, it has been posited that FMT could reflect effortful control over task performance (Holroyd & Umemoto, 2016; Umemoto, Inzlicht, & Holroyd, 2018). More generally, these results therefore suggest that the RewP ERP component and FMT power can capture partly dissociable effects during FB processing.

In a previous EEG study (Gheza, De Raedt, et al., 2018), we assessed whether these two electrophysiological components could also reflect the integration of reward with effort during a simple decision making task. Specifically, we conjectured that the RewP component, which is closely associated with reward processing, could reflect subjective reward evaluation arising from the integration of reward with effort information (i.e., the input to dACC). Moreover, we hypothesized that because FMT power reflects the need for cognitive control (Cavanagh & Frank, 2014) and/or sustained effortful control (i.e., the output from the dACC; Holroyd & Umemoto, 2016), the anticipation of effort could increase it. To test these predictions, participants performed a gambling task in which FB processing for two trial types was systematically compared: (i) regular trials, in which they could simply win or not a small monetary reward after gambling, and (ii) special trials, that differed from regular trials insofar they were informed beforehand by means of a specific visual cue that, in case of no-reward outcome after gambling, they were given the opportunity to redo it. However and critically, redoing the gambling task, after they freely chose to do so, entailed additional effort because a dot-clicking task had to be completed first. Hence, we operationalized effort as the combination of supplementary work (the dot-clicking task) with the associated opportunity cost (Kurzban, Duckworth, Kable, & Myers, 2013) implied in spending additional time for it. EEG results showed that the RewP component was larger for reward FB in special compared to regular trials, despite the fact that for both of them the same amount of money was actually earned, and that both trials ended after this specific outcome. In the time-frequency domain, Delta (Bernat, Nelson, & Baskin-Sommers, 2015) and Beta-gamma power (Cohen, Elger, & Ranganath, 2007; Mas-Herrero, Ripollés, HajiHosseini, Rodríguez-Fornells, & Marco-Pallarés, 2015) showed the same effect as the RewP (i.e., relief for effort avoidance). In comparison, effort anticipation did not influence FMT power, that only varied depending on FB outcome (being larger for no-

reward than reward, irrespective of the trial type). These results suggested that reward processing was increased when effort was anticipated but could be avoided, in line with the effort-discounting framework. More specifically, devaluation of reward is usually observed when a rewarding outcome (Botvinick et al., 2009) or action (Croxson et al., 2009; Prevost et al., 2010) is associated with effort, and here a symmetrical effect was reported (i.e. relief: increased reward processing in case of effort avoidance). However, a main limitation of this study was that regular and special trials also differed for the choice behavior. As a matter of fact, only special trials required participants to choose whether to redo or not the gamble upon the encounter of the no-reward outcome. Accordingly, the ERP results for the RewP were potentially confounded by this asymmetry in task demands. Moreover, in special trials, the choice presentation also hindered the contingency between no-reward FB and the effort task, and the effort task itself did not require specific cognitive demand or preparation. These limitations possibly explained the lack of FMT power increase after no-reward FB in special compared to regular trials.

In the current study we aimed at testing the specific influence of cognitive effort anticipation on reward FB processing, while controlling for temporal aspects (i.e., opportunity costs) and in the absence of choice. Using the same gambling task, we compared reward processing between two conditions that were matched for their task demands and choice behavior, and only differed in the amount of cognitive effort involved, being either small (easy task) or large (hard task). Effort was manipulated by means of an orthogonal mental arithmetic task that was either easy or hard (see Vassena et al., 2014 for a similar manipulation), which participants had to perform upon no-reward FB. Hence, unlike our previous experiment (Gheza, De Raedt, et al., 2018), no-reward outcome was always followed by the immediate presentation of an orthogonal mental arithmetic task, and no choice was thus required from the participants. Importantly, at the beginning of each trial, participants were informed about the actual

difficulty level of the upcoming mental arithmetic task (conditional to no-reward FB).

This novel design was used in two experiments. In Experiment 1, we focused on subjective ratings for the FB collected from 23 participants to assess whether our manipulation was successful, i.e. reward was judged as more positive if higher effort (hard compared to easy mental arithmetic task) was anticipated but could be avoided. In Experiment 2, we recorded 64 channel EEG in a new sample of participants while they performed the gambling task, as well as the ensuing mental arithmetic task in case no-reward occurred with the first gambling task. In line with our previous study (Gheza, De Raedt, et al., 2018), we hypothesized that the reward FB (never followed by the mental arithmetic task) after gambling would be judged as more positive if a hard compared to easy (mental arithmetic) task was anticipated. Symmetrically, the no-reward FB should be judged as more negative if a hard compared to easy task was anticipated. At the EEG level, we expected a larger RewP component, as well as increased power in the Delta and Beta-gamma bands, for the reward FB after gambling if a hard compared to easy task was anticipated. Moreover, we predicted that for the no-reward FB (signaling an ensuing mental arithmetic task), FMT power should increase for hard compared to easy trials, reflecting the need for cognitive control. We also ran exploratory EEG analyses at the cue level (i.e., effort anticipation), as well as during the execution of the effort task itself (i.e., effort exertion). Last, we also explored whether effort could influence the processing of the last FB, given after the completion of the mental arithmetic task. Although cognitive effort is generally perceived as costly and aversive (Apps et al., 2015; Kool, McGuire, Rosen, & Botvinick, 2010), reward processing is usually increased if reward is obtained after high compared to low effort exertion ("effort paradox"; Inzlicht, Shenhav, & Olivola, 2018). Accordingly, we hypothesized a larger RewP for reward FB obtained after the hard compared to easy mental arithmetic task (Ma, Meng, Wang, & Shen, 2013;

Wang, Zheng, & Meng, 2017). To test these hypotheses, we used Bayesian model comparisons (Rouder, Morey, Verhagen, Swagman, & Wagenmakers, 2017). This approach allowed us to fit and compare models of increased complexity for both behavioral and EEG data, and eventually to quantify the evidence in favor or against each of the listed hypotheses in terms of relative likelihood between models.

3. Methods

3.1. Participants.

Twenty-three undergrad students from Ghent University (17 females; median age: 21 years, range: 18-30) freely participated in Experiment 1 (behavioral only). They had normal or corrected-to-normal vision and did not report any history of neurological or psychiatric disorders. Sample size was determined to be at least as large as in our previous experiment (Gheza, De Raedt, et al., 2018) where a similar experimental manipulation was used, and where a significant effect of cost anticipation on reward was found (increased pleasantness [$p = .008$, $d = 0.57$] and relief [$p = .033$, $d = 0.27$] of reward when cost could be avoided).

Thirty-one young adults freely participated in Experiment 2 (behavioral + EEG). None of them participated in Experiment 1. Sample size was determined to be at least as large as in our previous EEG study where effects of cost anticipation on reward was found at the electrophysiological level (Gheza, De Raedt, et al., 2018). Two participants were excluded from further analyses, one due very noisy EEG recording, and the other one due to partial misunderstanding of the task instructions. The final sample consisted of 29 participants (17 females; median age: 24 years, range: 20-30).

These two experiments were part of a more general research project investigating effects of motivation on reward that was approved by the local ethics committee at Ghent University. All participants gave written informed consent prior to the start of the experiment, were debriefed at the end, and received a monetary compensation for their participation.

3.2. Stimuli and task.

For Experiment 1, we adapted a widely used gambling task (Gheza, De Raedt, et al., 2018; Hajcak, Moser, Holroyd, & Simons, 2007) and combined it with a previously used cognitive effort task (Vassena et al., 2014). At the beginning of each trial, participants were informed about the cognitive effort level with a text cue located at the center of the screen (1000 ms). More specifically, the word “easy” or “hard” was presented. Following a fixation dot (1500 ms), four doors appeared on the screen, and participants had to choose one of them by pressing with their left hand the corresponding numeric key (1 to 4) on a keyboard. After another fixation dot (700 ms), this choice was followed by an “evaluative” FB (1000 ms), indicating either a reward (green “+”) of 6 cents, or a neutral no-reward outcome (red “o”). Participants were instructed to guess and select a door containing a reward in order to maximize their payoff. Unbeknown to them, the outcome was unrelated to their actual choices but reward probability was set to 50%. Participants were instructed that in case of reward FB, the trial would end and a new one would follow. Hence, no additional effort was necessary. However, in case of no-reward FB, a second task would follow, which could be hard or easy (as indicated by the previous cue). Thus, no-reward FB at the gambling task entailed the prospect of effort. More specifically, after 1000 ms (fixation), a mental arithmetic task started. Here after, we refer to it as the effort task. This task required participants to complete two calculations (two additions or an addition and a subtraction, all of which with single-digit numbers) (see Fig. 1). In the hard condition, every operation required carrying or borrowing. In the easy condition, none of the two operation required carrying or borrowing. This manipulation results in two distinct difficulty effects, as shown in previous studies (Vassena, Cobbaert, Andres, Fias, & Verguts, 2015; Vassena, Deraeve, & Alexander, 2019; Vassena, Gerrits, Demanet, Verguts, & Siugzdaite, 2018) and confirmed by subjective ratings (see results below). The effort task structure was as follows: a hash symbol indicated the start

(400ms); digits and arithmetic signs were then presented serially, each lasting 500ms and being interleaved with a blank slide (200ms); finally, two possible solutions were presented simultaneously, and the participants had to choose the correct one by pressing the corresponding key with the right hand (i.e. numeric keypad; “1” for the leftmost or “2” for the rightmost solution). They were instructed to select the correct answer as quickly as possible, with a time limit of 4000ms. After this choice, a blank slide was presented (1000 ms), followed by a new “performance” FB (1000 ms) that shared the same properties as the “evaluative” FB used for the preceding gambling task: either a reward (green “+”), indicating a correct response and a win of 6 cents, or a neutral no-reward feedback for incorrect responses (red “o”) was presented. Additionally, a FB indicating “no response detected” could appear in case of late or lack of response. During the effort task, a serial presentation was chosen in order to pace the processing of each digit and arithmetic sign between conditions, as well as to avoid calculation strategies (Vassena et al., 2014). Across trials, different combinations of digits and arithmetic signs were used to avoid learning or habituation. After the effort task, a new trial of the gambling task followed. The inter trial interval was fixed and set to 1000 ms.

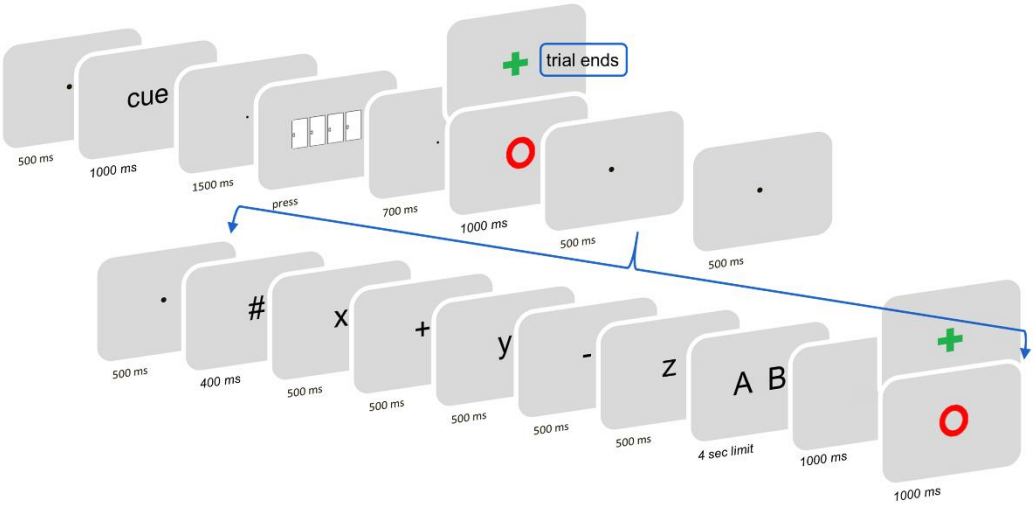


Figure 1. Overview of the task and trial structure. Participants were first informed about the cognitive effort level with a text cue (word “easy” or “hard”). After they picked one door, they received a reward or no-reward FB (50% reward probability). Only in case of no-reward FB after gambling, the effort task ensued. For both conditions, the initiation of the effort task was probed by an uninformative hash symbol (#). After it, a “performance” FB was given, being reward-related in case of correct execution of it (see main text for details). In a few trials, the subjective value of the first evaluative feedback (after gambling) was assessed with specific probes presented 1000 ms after its offset.

The subjective value of the first evaluative feedback (after gambling) was assessed by specific probes. In a few trials (n = 48), 1000 ms after the offset of the evaluative FB, three questions were presented, probing the perceived pleasantness, frustration and relief. Participants answered them using visual analog scales (VAS). These three ratings were submitted 12 times for each effort level (easy vs. hard) and outcome (reward vs. no reward) condition.

Experiment 1 consisted of 208 trials, including an equal amount of easy and hard trials. Because the first gambling task had a pre-set reward

probability of 50%, and the effort task had to be completed only in case of no-reward FB, the effort task was administered 52 times for each difficulty level.

Seven self-paced breaks were included throughout the experiment. At the end of each break, participants were asked to rate the difficulty of the effort task, its pleasantness, their motivation to complete it, and their satisfaction in performing correctly with it. Each question was submitted twice, for each of the two difficulty levels, using a VAS. Participants received a fixed €8 compensation for their participation. Depending on their accuracy with the effort task, a maximum payoff of €12,48 could be earned.

For Experiment 2, where 64-channel EEG was recorded, the same procedure was used but a few changes were made. The reward feedback with the gambling task entailed a 12 cents (instead of 6) win. The three ratings about feedback value were submitted each 32 times in total (instead of 48), 1000ms after the offset of the FB. For each difficulty level (easy vs. hard) and outcome (reward vs. no reward) condition, they were presented 8 times. Experiment 2 consisted of 224 trials, with an equal amount of easy and hard trials (112 each). For each of them, there were 56 trials where the effort task had to be performed. Participants were compensated €15 for their participation. Depending on their accuracy with the effort task, they could earn up to €26,88.

The experiments' duration was approximately 60 minutes, including instructions and a short practice. For Experiment 2, the EEG preparation lasted 30 minutes on average. All stimuli were shown against a grey homogenous background on a 21-in CRT screen and controlled using E-Prime (V 2.0, Psychology Software Tools Inc., Sharpsburg, PA).

3.3. Behavioral data analysis.

We evaluated the effectiveness of the cognitive effort manipulation by comparing performance on the effort task (i.e., accuracy and speed) between the easy and hard conditions. Moreover, we also compared their subjective value by analyzing the ratings of difficulty, pleasantness, motivation to perform well, and pleasure in performing well. These ratings were first transformed to percentages, setting anchors to the boundaries of the scales, and were averaged across the seven repetitions.

At the FB level, the VAS scores obtained for each difficulty level (easy vs. hard), FB outcome (reward vs. no reward), and affective dimension (pleasantness, frustration or relief) were also first transformed to percentages, setting anchors to the boundaries of these scales. For the "frustration" scale, we revere-scored the percentages in order to provide comparable ratings for the three affective dimensions (all going from negative to positive).

3.4. Recording and processing of electrophysiological data.

In Experiment 2, EEG was recorded using a 64-channel Biosemi Active Two system (http://www.biosemi.com) which uses the Common Mode Sense (CMS) active electrode and Driven Right Leg (DRL) passive electrode as ground, and sampled at 512 Hz. Four additional electrodes measured horizontal and vertical eye movements (electro-oculogram, EOG). The EEG was preprocessed offline with custom scripts calling functions from EEGLAB 14.1.1 (Delorme & Makeig, 2004), implemented in Matlab R2013b. The commented scripts are available at https://osf.io/urzd9/. First, the continuous EEG signal was referenced to the averaged mastoids, and portions of recording affected by macroscopic artifacts were visually detected and rejected. The signal was then filtered

offline with separate high-pass 0.05 Hz and low-pass 35 Hz FIR filters, and an independent component analysis (ICA) was run on the continuous data. Individual epochs were extracted from -2000 to 2000 ms around the onset of the cue, the evaluative FB (after the initial gambling task), and the performance FB (after the subsequent effort task), and the pre time-locking event baseline was subtracted (-250 to 0 ms). Artefactual ICA components were manually selected focusing on eye artifacts and spatial or temporal discontinuities, and were removed from all segmented data. A semi-automatic artifact rejection procedure was applied to eliminate trials with i) voltage values exceeding ± 90 µV (-700 to 700 ms around the time-locking event), ii) abnormal linear trends with slope larger than ± 90 µV/epoch, iii) improbable data based on joint probability of electrode activities; a final visual inspection determined the final trials' inclusion.

At the level of the evaluative FB (gambling task), we extracted the RewP ERP component, as well as power changes in Theta (FMT), Delta and Beta-gamma ranges. FMT power was also extracted and analyzed at the Cue level. Finally, at the level of the performance FB (effort task), we analyzed the RewP component.

The RewP ERP component has often been defined as the lack of a N200 component elicited by no-reward FB, or alternatively, as a positive deflection that cancels it out (Gheza, Paul, et al., 2018; Holroyd et al., 2008). To score the RewP in an unbiased manner, we first identified the latency of the N200 for no-reward FB (240 ms). Second, based on this latency (± 25 ms), we assessed the topography of the difference wave between reward and no-reward, irrespective of effort (collapsed localizer approach; Luck & Gaspelin, 2017). This topography showed maximal amplitude values at channels FCz and Cz (Fig. 2). Given these electrophysiological properties, the RewP component was defined as the average ERP activity within the 215–265 ms interval following FB onset at these specific electrodes (for similar approaches, see Cockburn & Holroyd, 2018; Gheza, De Raedt, et al., 2018; Novak & Foti, 2015).

Time frequency analysis was done using EEGLAB built-in std_ersps() function, based on complex Morlet wavelet convolution (2 to 8.75 cycles, 0.8 to 35 Hz, 75 log spaced frequencies, 200 time points per epoch). The time interval -500 to -200 ms before the Cue or the FB onset was used for baseline normalization. FMT band power change (4 – 8 Hz) were defined as the mean within 200 – 400 ms, decibel (dB) converted (10*log10[power/baseline]) at FCz. The same approach was adopted for the estimation of Delta (0.8 – 3.9 Hz) and Beta-gamma (20 – 35 Hz) band power changes, defined respectively as the mean amplitude within 200 – 400 ms at a set of parietal sites (CPz, CP1, CP2, CP3, CP4) for Delta, and within 250 – 350 ms at a set of frontocentral sites (FCz, Fz, FC1, FC2) for Beta-gamma. Time windows and channel locations were based on the band-specific maximal power from the grand average of all conditions (Luck and Gaspelin, 2017; see Figs. 4, 6, 7).

3.5. Statistical analyses.

Behavioral data (subjective ratings) and each EEG component (RewP, FMT, Delta, or Beta-gamma power) were analyzed through Bayesian model comparison. Inference about their generative processes was based upon Bayes Factors (BFs), computed for alternative explanatory models in ANOVA designs (Rouder, Morey, Verhagen, Swagman, & Wagenmakers, 2017; see also Schindler, Schettino, & Pourtois, 2018). The analyses' pipeline was implemented in R v3.5.0 (R Core Team, 2017) with the package BayesFactor v0.9.12-4.2 (Morey & Rouder, 2015), and involved: I) defining theoretically sound probability models; II) computing BFs, i.e. the ratio between the likelihood of each model of interest (the probability of the observed data, given the model/hypothesis) and the likelihood of the null model; III) model selection based on the highest BF; the models' likelihood were estimated using Markov-Chain Monte Carlo simulations with 10,000 iterations, and BFs

were computed assuming a medium Cauchy prior centered on zero: d ~ Cauchy (0,.707). IV) Follow up contrasts by means of Bayesian t-test between conditions of interest were used to characterize the direction of the effects.

At the FB level, for both behavioral and electrophysiological data, the models of interest included the effects of: 1) outcome, 2) difficulty level, 3) outcome + difficulty level, 4) outcome x difficulty level. The null model was a simple intercept model. In addition, for the FB ratings, the effects of random factors participants, affective dimension, and their interaction were specified as nuisance in all the models (including the null). For the EEG data, all models included as nuisance the effect of the random factor participants.

At the cue level, we used a one tailed Bayesian t-test to estimate the amount of evidence in favor of a model specifying increased FMT power for high vs. low cognitive effort, as compared to a point-null model.

Similarly, at the level of the performance FB, we used a one tailed Bayesian t-test to estimate the evidence in favor of increased RewP amplitude for high vs. low effort, as compared to a point-null model. In this analysis, we only used reward FB as participants made very few errors with the effort task, and hence eventually received no-reward as FB very seldom (see results below).

4. Results

4.1. Experiment 1.

The accuracy for the effort task was higher for the easy (m = 98 %, SD = 14) compared to the hard condition (m = 87 %, SD = 34; BF+0 = 2.20 x 103). Mean reaction time was larger for the hard (m = 1091 ms, SD = 476) compared to the easy condition (m = 621 ms, SD = 144; BF+0 = 4.11 x 103).

At the subjective level, these two difficulty levels were experienced as clearly different. The hard compared to easy condition was associated with increased difficulty (M easy = 6.1, SD = 7.3; M hard = 31.2, SD = 18.7; BF-0 = 1.09 x 105) and reduced pleasantness (M easy = 83.4, SD = 12.5; M hard = 62.7, SD = 21.0; BF+0 = 1.92 x 103), while participants reported similar levels of motivation to perform them correctly (M easy = 85.1, SD = 14.8; M hard = 86.6, SD = 13.6; BF01 = 3.58), as well as pleasure in performing them correctly (M easy = 81.8, SD = 17.1; M hard = 76.4, SD = 18.5; BF01 = 2.00).

The FB ratings were best explained by the outcome x difficulty level interaction model, under which the observed data were BF10 = 5.62 x 10648 times more likely to be produced than under the null model. The interaction model outcome x difficulty level explained the observed data 325 times better than the second-best model, including the main effect of outcome alone. Follow up Bayesian one-tailed t-tests showed strong evidence for the hypothesis that, for no-reward outcome, the FB in low-effort trials was evaluated as more positive than the same FB delivered in high-effort trials (BF+0 = 6.00 x 105); conversely, for reward outcome, the hypothesis of more positive evaluations for the FB in the high- vs. low-effort trials (compared to a point-null hypothesis) was weakly supported (BF+0 = 2.22). In other words, participants rated the no-reward FB as more positive when they anticipated low- vs high- effort.

4.2. Experiment 2.

Similarly to Experiment 1, the accuracy for the effort task was higher for the easy (m = 99 %, SD = 12) compared to the hard condition (m = 88 %, SD = 32; BF+0 = 1.21 x 106). Mean reaction time was larger for the hard (m = 1037 ms, SD = 339) compared to the easy condition (m = 602 ms, SD = 119; BF+0 = 8.97 x 106).

At the subjective level, these two difficulty levels were again experienced as clearly different. The hard compared to easy condition was associated with increased difficulty (M easy = 13.1, SD = 15.1; M hard = 42.1, SD = 21.1; BF-0 = 2.20 x 105) and reduced pleasantness (M easy = 72.0, SD = 22.4; M hard = 57.7, SD = 20.9; BF+0 = 21.5). At variance with Experiment 1, participants reported lower levels of motivation to perform correctly the easy vs. hard condition (M easy = 70.3, SD = 25.2; M hard = 81.8, SD = 16.5; BF-0 = 177.9), while ratings for pleasure in performing them correctly were similar (M easy = 68.7, SD = 22.9; M hard = 71.5, SD = 16.5; BF01 = 3.65).

In line with Experiment 1, the FB ratings were best explained by the outcome x difficulty level interaction model, under which the observed data were BF10 = 5.48 x 10269 times more likely to be produced than under the null model. The interaction model outcome x difficulty level explained the observed data 13252 times better than the second-best model, including the additive effects of outcome + difficulty level, and 17202 times better than the model including the main effect of outcome alone. The follow up Bayesian one-tailed t-tests showed strong evidence for the hypothesis that, for no-reward outcome, the FB in low-effort trials was evaluated as more positive than the same FB delivered in high-effort trials (BF+0 = 2.55 x 107). Conversely, for reward outcome, there was no conclusive evidence for the hypothesis of more positive evaluations for the FB in the high- vs. low-effort trials (BF+0 = 0.81). Replicating Experiment

1, participants rated the no-reward FB as more positive when they anticipated low- vs high- effort.

4.2.1. RewP.

At the FB level (gambling task), amplitude variations of the RewP component across conditions were best explained by the models outcome (BF10 = 1.68 x 1017) and outcome + difficulty level (BF10 = 9.20 x 1016), relative to the null. Direct comparison of these two models did not provide conclusive evidence in favor of the simple model outcome (BF = 1.82), while both the simple model outcome and the additive model outcome + difficulty level explained the observed data better than the interaction model outcome x difficulty level (BF = 9.90 and BF = 5.43, respectively). Follow up one-tailed Bayesian t-tests, within each of these two factors' levels separately, showed strong evidence in favor of larger RewP amplitude for reward than no-reward outcome (BF+0 = 8.22 x 1012), and moderate evidence for larger RewP amplitude for high compared to low effort (BF+0 = 14.39). Hence, the RewP component showed larger amplitudes for reward than no-reward FB, and for high compared to low effort (Fig. 2).

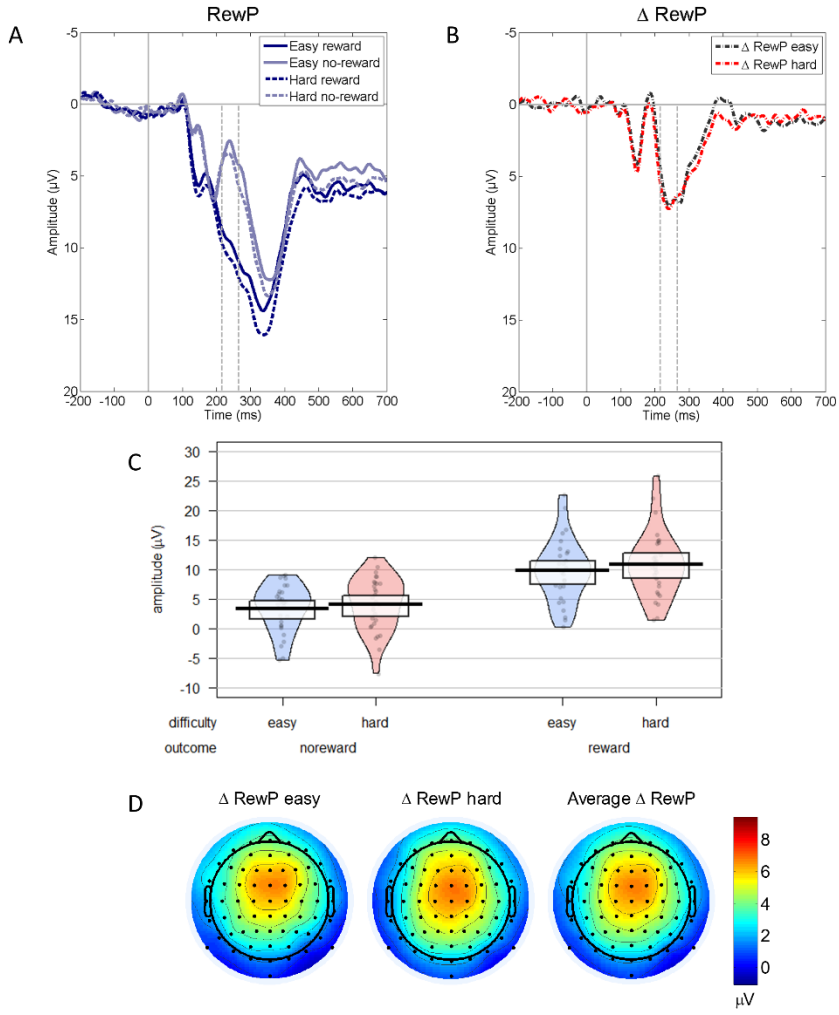


Figure 2. RewP results for evaluative FB. (A) RewP for easy (solid lines) and hard (dashed lines) effort task, separately for reward (dark blue) and no-reward (light blue) outcome. (B) Corresponding difference waves for the two difficulty levels (easy: black line; hard: red line) obtained after the ERP activity of no-reward was subtracted from reward. The RewP was computed as the average amplitude at Cz and FCz within the 215-265 ms interval post-feedback onset (highlighted by the dashed vertical grey lines). (C) Amplitudes of the RewP as a function of difficulty level and FB outcome. The RewP was larger for reward compared to no-reward FB, and for hard compared to easy effort task. Horizontal black lines indicate mean amplitude values, white boxes cover the 95% highest density interval (HDI), and gray dots represent individual subject values. (D) Horizontal topographies (top view) of the difference waves (reward minus no-reward), averaged from 215 to 265 ms after FB onset, for easy (left) and hard (right) difficulty level.

At the level of the performance FB (effort task), variations of the RewP's amplitude across conditions was best explained by the model assuming larger values for high compared to low effort (BF+0 = 37.37), relative to a null model assuming no difference. In other words, the RewP increased for reward feedback associated with the execution of the hard relative to the easy condition (Fig. 3).

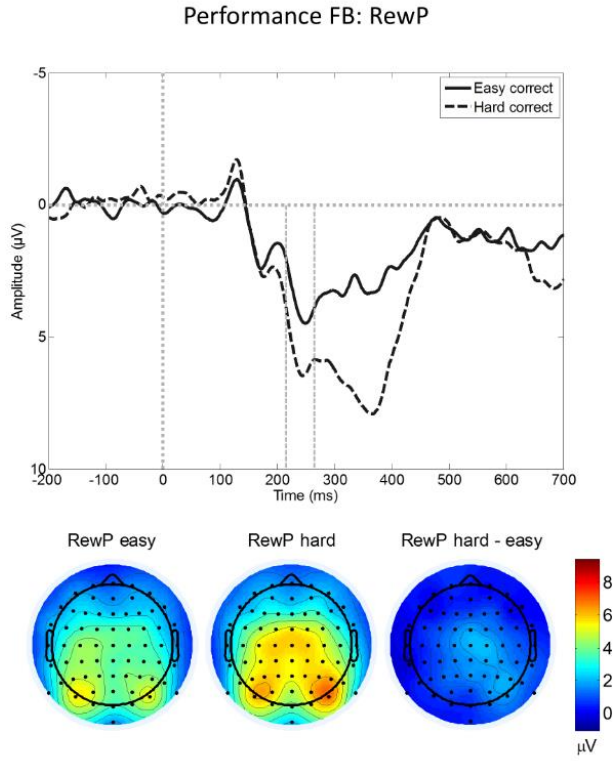
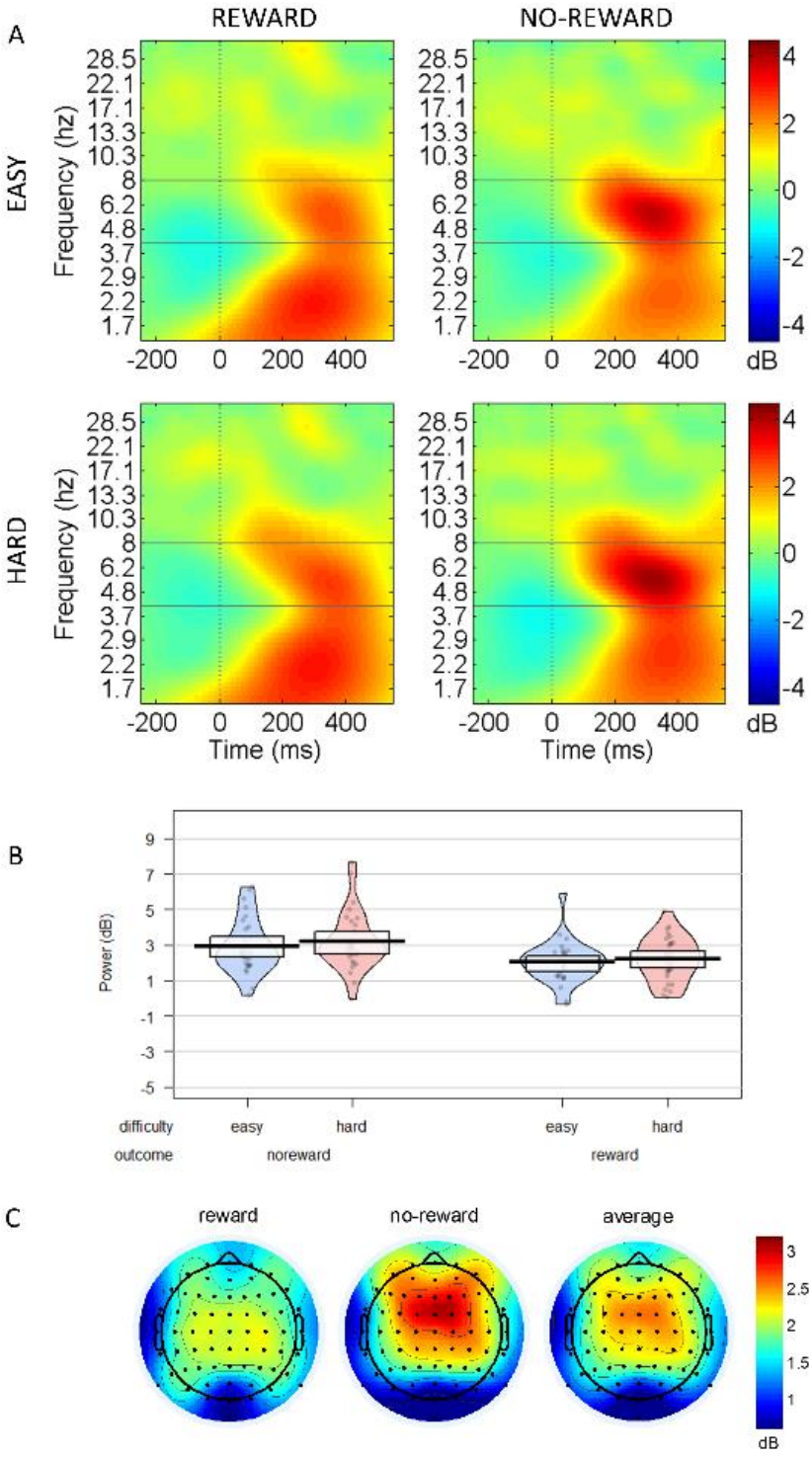


Figure 3. RewP results for performance FB. (A) Grand average ERP waveforms from Cz and FCz pooled together, showing the RewP for reward FB (correct response) after execution of the easy (solid lines) or hard (dashed lines) effort task. The RewP was computed as the average amplitude at Cz and FCz within the 215-265 ms interval post-feedback onset (the corresponding time-window for amplitude measurement and scoring is highlighted by the dashed vertical grey lines). The RewP was larger for reward FB obtained after the hard compared to easy mental arithmetic task.

4.2.2. FMT power.

At the FB level (gambling task), FMT power was best explained by the model outcome when compared to the null model (BF10 = 5.72 x 105) and to the interaction model outcome * difficulty level (BF = 12.61). There was weaker evidence in favor of the model outcome relative to the additive model outcome + difficulty level (BF = 2.51). Follow up one-tailed Bayesian t-tests between outcome levels showed strong evidence in favor of larger FMT power for no-reward than reward outcome (BF+0 = 1.48 x 105), compared to a point-null hypothesis. Accordingly, FMT power was larger for no-reward compared to reward FB, without modulation by effort though (Fig. 4).

(right) Figure 4. FMT results for evaluative FB. (A) FMT (4-8 Hz) power changes from electrode FCz, comparing reward and no-reward FB, for easy vs. hard difficulty level. (B) FMT power changes as a function of difficulty level and FB outcome, showing a main effect of FB outcome, translating larger power values for no-reward than reward FB. Horizontal black lines indicate mean amplitude values, white boxes cover the 95% highest density interval (HDI), and gray dots represent individual subject values. (C) Horizontal topographies (top view) of the average FMT power change computed in the 200-400 ms window following FB onset.


A
REWARD
NO-REWARD
EASY
HARD
Frequency (hz)
28.5
22.1
17.1
13.3
10.3
8
6.2
4.8
3.7
2.9
2.2
1.7
-200
0
200
400
Time (ms)
4
2
0
-2
-4
dB
B
Power (dB)
9
7
5
3
1
-1
-3
-5
difficulty
easy
hard
outcome
noreward
reward
C
reward
no-reward
average
3
2.5
2
1.5
1
dB

At the cue level (Fig. 5), weak evidence was obtained in favor of the null hypothesis stating no difference in FMT power between high and low effort, relative to the alternative hypotesis positing a larger FMT power for high vs. low effort (BF0+ = 2.35).

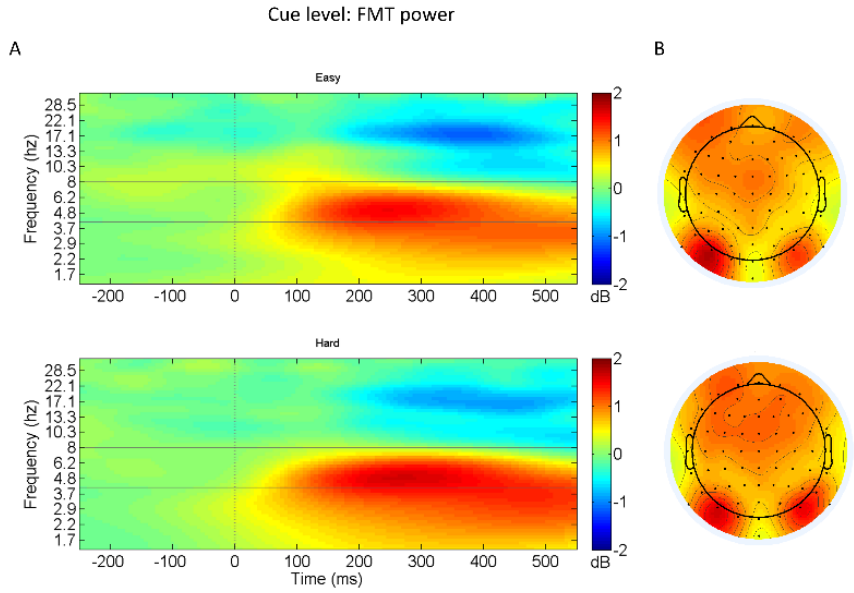
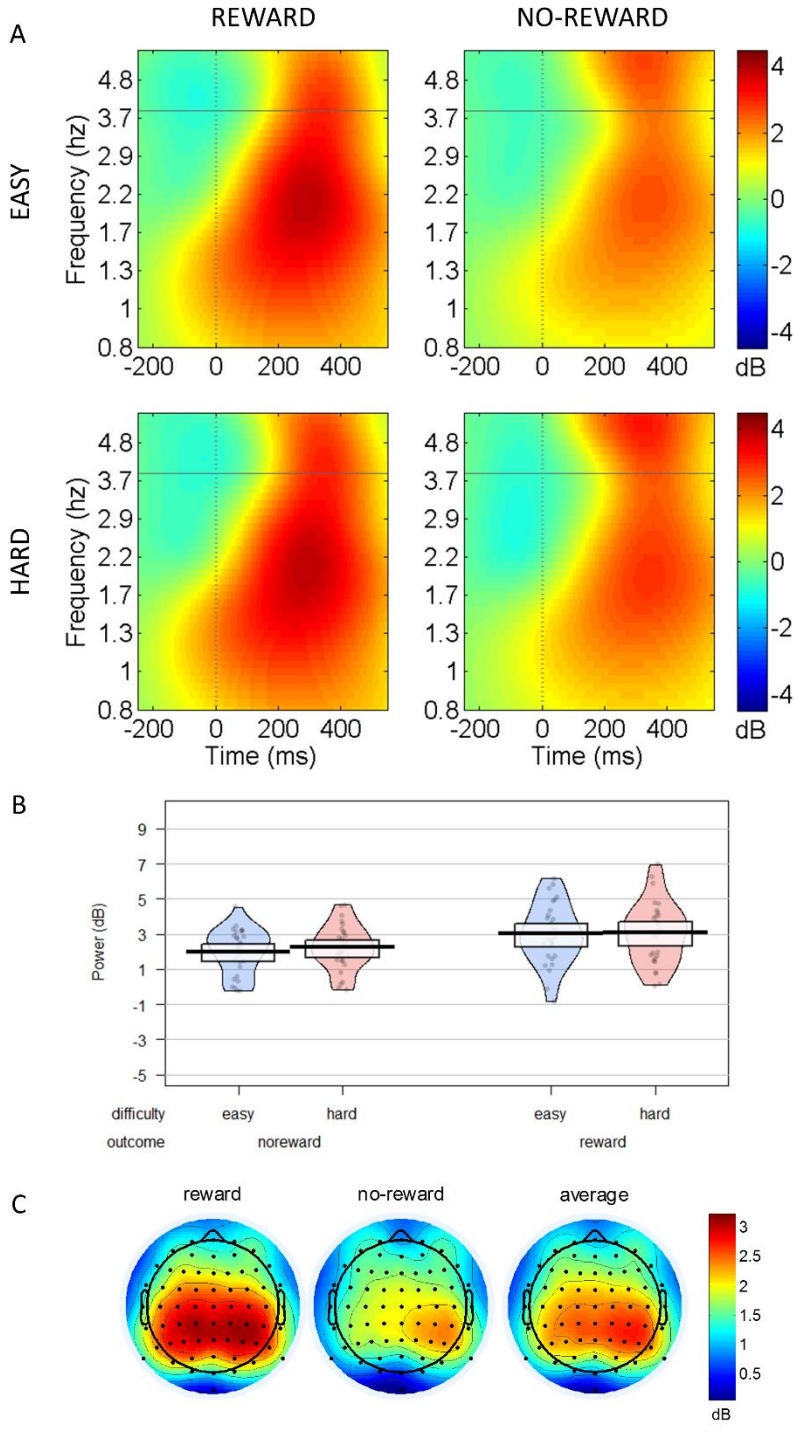


Figure 5. FMT results at the cue level. (A) FMT (4-8 Hz) power changes from electrode FCz, comparing the cue presentation for the two difficulty levels ("easy" vs "hard" word presentation). (B) Horizontal topographies (top view) of the average FMT power change computed in the 200-400 ms window following cue onset, for easy (top) and hard (bottom) cue presentation.

4.2.3. Delta power.

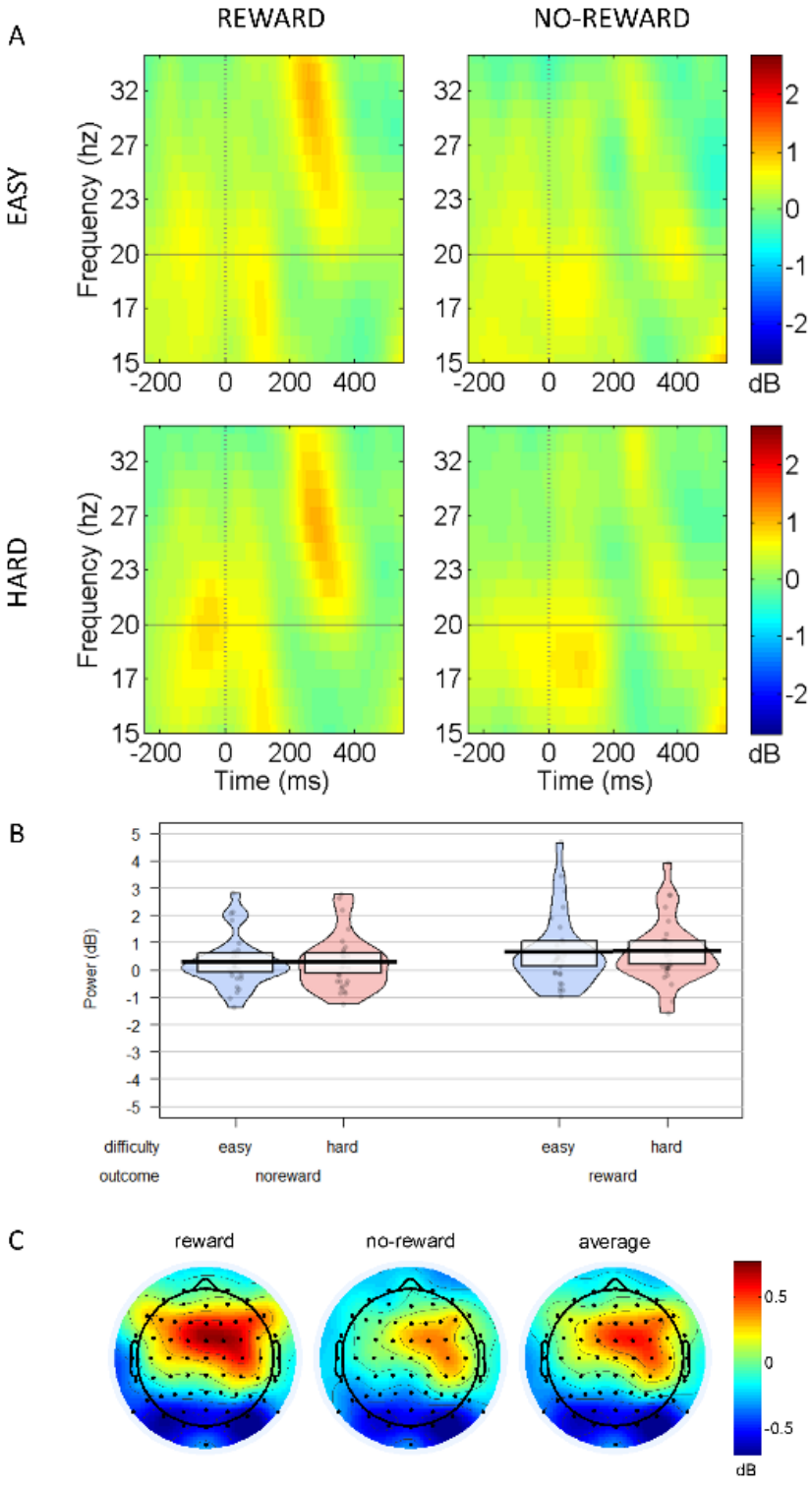
At the FB level (gambling task), Delta power was best explained by the model outcome when compared to the null model (BF10 = 3.57 x 105). The model outcome was also better relative to the second best-model outcome + difficulty level (BF = 4.40) and to the interaction model outcome * difficulty level (BF = 18.80). Follow up one-tailed Bayesian t-tests between outcome levels showed strong evidence in favor of larger Delta power for reward than no-reward outcome (BF+0 = 3.05 x 105), compared to a point-null hypothesis. Symmetrically to FMT, Delta power was larger for reward compared to no-reward FB, without any modulation by effort (Fig. 6).


A
REWARD
NO-REWARD
EASY
HARD
Frequency (hz)
4.8
3.7
2.9
2.2
1.7
1.3
1
0.8
-200
0
200
400
Time (ms)
dB
4
2
0
-2
-4
B
Power (dB)
9
7
5
3
1
-1
-3
-5
difficulty
easy
hard
outcome
noreward
reward
C
reward
no-reward
average
3
2.5
2
1.5
1
0.5
dB

(left) Figure 6. Delta results for evaluative FB. (A) Delta (0.8-3.9 Hz) power changes from centro-parietal electrodes (CPz, CP1, CP2, CP3, and CP4 collapsed), comparing reward to no-reward FB, for easy vs. hard difficulty level. (B) Delta power changes as a function of difficulty level and FB outcome, showing a main effect of FB outcome only, translating larger power values for reward than no-reward FB. Horizontal black lines indicate mean amplitude values, white boxes cover the 95% highest density interval (HDI), and gray dots represent individual subject values. (C) Horizontal topographies (top view) of the average Delta power change computed in the 200-400 ms window following FB onset.

4.2.4. Beta-gamma power.

At the FB level (gambling task), Beta-gamma power was best explained by the model outcome when compared to the null model (BF10 = 44.71). It also explained the observed data better relative to the additive model outcome + difficulty level (BF = 6.74), and to the interaction model outcome * difficulty level (BF = 34.83). Follow up one-tailed Bayesian t-tests between outcome levels showed strong evidence in favor of larger Beta-gamma power for reward than no-reward outcome (BF+0 = 73.70), compared to a point-null hypothesis. Similarly to Delta, Beta-gamma power was larger for reward compared to no-reward FB, without modulation by effort (Fig. 7).


A
REWARD
NO-REWARD
EASY
HARD
Frequency (hz)
32
27
23
20
17
15
-200
0
200
400
Time (ms)
2
1
0
-1
-2
dB
B
Power (dB)
5
4
3
2
1
0
-1
-2
-3
-4
-5
difficulty
easy
hard
outcome
noreward
reward
C
reward
no-reward
average
0.5
0
-0.5
dB

(left) Figure 7. Beta-gamma results for evaluative FB. (A) Beta-gamma (20-35 Hz) power changes from fronto-central electrodes (FCz, FC1, FC2, and Fz collapsed), comparing reward and no-reward FB, for easy vs. hard difficulty level. (B) Beta-gamma power changes as a function of difficulty level and FB outcome, showing a main effect of FB outcome only, translating larger power values for reward than no-reward FB. Horizontal black lines indicate mean amplitude values, white boxes cover the 95% highest density interval (HDI), and gray dots represent individual subject values. (C) Horizontal topographies (top view) of the average Beta-gamma power change computed in the 250-350 ms window following FB onset.

5. Discussion

In this study, we sought to replicate and extend the outcome of a previous EEG study (Gheza, De Raedt, et al., 2018) where we found that reward processing was transiently increased when effort was anticipated, but could be avoided. This effect was found at the subjective and EEG levels. More specifically, subjects reported more pleasure and relief for a reward FB when effort was anticipated but could eventually be avoided, compared to the situation where effort was not involved. The RewP ERP component, which is generated in the dACC (Gehring & Willoughby, 2002; Miltner, Braun, & Coles, 1997; Smith et al., 2015), as well as Delta and Beta-gamma power (Bernat et al., 2015; Mas-Herrero et al., 2015), were all increased in this former compared to latter condition. These results suggested that early on, following FB onset, reward and effort information integrated with one another. More generally, they were also compatible with the assumptions of the HRL-ACC theory positing that the dACC processes the reward value of the task or actions, to eventually determine the level of cognitive control to be exerted (Holroyd & Umemoto, 2016; Holroyd & Yeung, 2012). However, besides effort, task demands (including choice behavior) were not properly balanced between these two conditions, which could have introduced a confound in their direct comparison. To overcome this limitation, we amended the experimental design, removed the choice, and set up two conditions that differed regarding cognitive effort exclusively, manipulated through the difficulty of an orthogonal mental arithmetic task that was either easy or difficult. More specifically, participants performed a gambling task (Gheza, De Raedt, et al., 2018; Hajcak, Holroyd, Moser, & Simons, 2005; Paul & Pourtois, 2017) and were cued beforehand that upon no-reward after gambling, a mental arithmetic task had to be completed to end the trial, whose difficulty level was either easy or hard (Vassena et al., 2014). This manipulation allowed us to directly compare reward processing when either an easy or hard task was anticipated, but eventually avoided. Based on our previous study

(Gheza et al., 2018) and available literature (Croxson et al., 2009; Umemoto et al., 2018; Vassena et al., 2014), we surmised that the RewP component should be larger for reward if a hard relative to easy effort task was anticipated, hence if a high compared to low effort task could be avoided. We also hypothesized that participants would report more pleasure and relief in this former compared to latter condition. A number of new findings emerge from this study and are discussed here after.

First, the behavioral results for the effort task (Experiments 1&2) confirmed that the manipulation was successful. As expected, participants made more errors and were slower in the hard compared to the easy mental arithmetic task. However, accuracy was high for the hard effort task, which was an important prerequisite to minimize possible differences between conditions in terms of reward probability, besides effort. In other words, the hard effort task was more difficult than the easy one, but not necessarily associated with more uncertainty about self-efficacy and reward probability. Moreover, in both experiments alike, subjective ratings confirmed that participants reported more difficulty and less pleasantness for the hard compared to the easy mental arithmetic task, suggesting that these two levels were indeed perceived as distinct by them. These results are compatible with the notion that cognitive effort is usually perceived as aversive (Apps et al., 2015; Shenhav et al., 2017; Westbrook et al., 2013), Importantly, motivation and pleasure in performing it correctly were balanced between the two conditions.

When focusing on the subjective evaluation of the FB itself, in both experiments alike, participants rated the no-reward FB as less positive (i.e., more frustrating) when high compared to low effort was anticipated. However, evidence for a symmetrical modulation of reward FB (i.e., more pleasant when high compared to low effort was anticipated) was weak only. Hence, effort anticipation appeared to influence mostly the no-reward outcome in the current study, whereas the opposite effect was found in our previous study. Accordingly, at the subjective level, the elected effort

manipulation seemed to increase negative affect (frustration), while positive affect (pleasure and relief) was only weakly influenced by it, which contrasts with the effect found in our previous study (Gheza, De Raedt, et al., 2018). However, this result suggests that effort anticipation did influence the way the evaluative feedback (no-reward) after gambling was perceived by participants, with high effort increasing its negative subjective value.

At the EEG level (Experiment 2), for each of the reward-related components considered (RewP, Delta, and Beta-gamma power), we found strong evidence for their modulation by FB outcome, as previously reported in the literature (Bernat et al., 2015; Cavanagh, 2015; Cohen et al., 2007; Gheza, De Raedt, et al., 2018; Mas-Herrero et al., 2015; Proudfit, 2015). The RewP was clearly larger for reward than no reward FB, and Beta-gamma as well as Delta power showed the same effect. Conversely, FMT power was larger for no-reward than reward FB. However, for all these EEG components, we failed to find a significant interaction effect between outcome and difficulty level. Hence, we did not confirm our main hypothesis assuming that reward processing at the RewP level could be enhanced when high effort was anticipated but could eventually be avoided after the initial gambling task.

Whereas the RewP did not show the hypothesized interaction effect, this component was however larger when high compared to low effort was anticipated, but irrespective of the FB outcome. Speculatively, this effect may translate a general increase in attention or monitoring processes occurring at the FB level following gambling, in case high effort was anticipated. Nevertheless, this change was not stronger for reward compared to no-reward, challenging the assumption that reward processing scaled up by effort avoidance at that level. Hence, for the FB provided after gambling, we found no evidence of a clear integration of effort with reward information. However, additional analyses suggested that integration of effort with reward did occur at a later time during the

course of the trial, but that at the very beginning of the trial, effort information per-se was weakly processed. More specifically, at the cue-level, FMT power was weakly modulated by effort anticipation (i.e., it was not larger for “hard” vs. “easy” cue presentation). However and importantly, at the level of the performance FB following the effort task (hence at the very end of the trial), the RewP was clearly larger for reward obtained after the hard compared to easy mental arithmetic task, suggesting increased reward processing after effort exertion. Accordingly, although integration between reward and effort did not occur at the FB level following gambling, it took place later during the trial, after the completion of the effort task. Thus, although we failed to find increased reward processing accompanying effort avoidance at the FB after initial gambling (Gheza, De Raedt, et al., 2018), we found enhanced reward processing later on during the course of the trial, after the successful completion of a hard compared to easy task (Ma et al., 2013; Wang et al., 2017; see also Schouppe et al., 2014;).

Tentatively, several methodological factors could explain this apparent shift in time of the likely integration between effort and reward, compared to our previous study (Gheza et al., 2018). First, although the two difficulty levels were performed and experienced as such by the participants, we cannot exclude the possibility that the contrast between them was eventually subtle. Accordingly, cognitive effort was either low or high depending on the difficulty level implied, but perhaps not sufficiently different to swiftly influence reward processing (the RewP amplitude) at the level of the first FB provided after gambling. Second, unlike our previous study where participants could freely choose to encounter effort after no-reward (Gheza, De Raedt, et al., 2018), here the effort task was made fully contingent on no-reward FB, thereby removing choice behavior. Presumably, in these circumstances, proactive control processes active during the gambling task, and involved in the prospective integration of reward with cost information, were strongly attenuated, and a reactive

guidance was promoted instead, mostly active during the processing of the FB following gambling in case of no-reward outcome. According to the dual mechanisms of control framework (Braver, 2012), proactive control is defined as the sustained and anticipatory maintenance of goal-relevant information within the lateral prefrontal cortex to enable optimal cognitive performance. Accordingly, integrating reward with effort information on beforehand may only be meaningful when it can be instrumental to swiftly make a decision on whether or not to exert the effort (Gheza, De Raedt, et al., 2018). Instead, in this study it is likely that participants only started to process actively the effort information after the first FB and in case of no-reward, hence when the mental arithmetic task was initiated. In agreement with this view, we found that FMT power did not discriminate the two main conditions (easy vs. hard) at the beginning of the trial (cue-level). In this context, integration of effort with reward did occur, but a late stage however, namely when the (last) FB was provided after the completion of the effort task, and where reward processing was clearly increased at the RewP level in case a hard compared to easy task had just been executed successfully.

All in all, our results therefore confirm that the RewP ERP component can capture important monitoring effects during FB processing that likely reflect the integration of reward with effort information. Here we report evidence for a relatively late integration effect between effort and reward occurring at the very end of the trial (as opposed to early on, following the first gambling task), probably because at that level effort information was used reactively by participants to gauge reward processing. More generally, because the RewP has been linked to the dACC (Becker, Nitsch, Miltner, & Straube, 2014; Gehring & Willoughby, 2002; Miltner et al., 1997; Smith et al., 2015), our new results add to the existing cognitive neuroscience literature showing that this medial frontal region likely contributes to a swift integration between reward and effort during FB

processing and hence decision making (Botvinick et al., 2009; Croxson et al., 2009; Prevost et al., 2010; Vassena et al., 2014, 2017).

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Chapter 5: Abnormal approach-related motivation but spared reinforcement learning in MDD[1]

[1] Gheza, D., Bakic, J., Baeken, C., De Raedt, R., & Pourtois, G. (2019). Abnormal approach-related motivation but spared reinforcement learning in MDD: Evidence from fronto-midline Theta oscillations and frontal Alpha asymmetry. Cognitive, Affective, & Behavioral Neuroscience.

1. Abstract

Major depression is characterized by abnormal reward processing and reinforcement learning (RL). This impairment might stem from deficient motivation processes, in addition to reduced reward sensitivity. In this study, we recorded 64-channel EEG in a large cohort of major depressive disorder (MDD) patients and matched healthy controls (HC) while they performed a standard RL task. Participants were asked to discover, by trial and error, several hidden stimulus-response associations having different reward probabilities, as enforced using evaluative feedback. We extracted induced fronto-midline Theta (FMT) power time-locked to the response and feedback as neurophysiological index of RL. Furthermore, we assessed approach-related motivation by measuring frontal alpha asymmetry concurrently. At the behavioral level, MDD patients and HCs showed comparable RL. At the EEG level, FMT power systematically varied as a function of reward probability, with opposing effects found at the response and feedback levels. Although this global pattern was spared in MDD, at the feedback level these patients showed however a steep FMT power decrease across trials when reward probability was low. Moreover, they showed impaired approach-related motivation during task execution, as reflected by frontal Alpha asymmetry. These results suggest a dissociation between (globally spared) RL and (impaired) approach motivation in MDD.

2. Introduction

Leading the world burden of diseases (Greden, 2001; Kessler & Bromet, 2013), MDD encompasses a spectrum of psychological and somatic impairments which give rise to a large heterogeneity in terms of symptomatology, clinical course, and responsiveness to treatment. However, across all depression subtypes, a causal role in the etiology and maintenance of this disorder is usually attributed to a "diminished interest or pleasure in all, or almost all, activities" and "lack of reactivity to usually pleasurable stimuli" (DSM-V; APA, 2013), commonly referred to as anhedonia.

Several research lines have identified reward processing as a key deficit in depression, putting forward anhedonia as a valid endophenotype of this emotional disorder (Hasler, Drevets, Manji, & Charney, 2004). Reward-related deficits in depression may correspond to alterations of multiple and non-overlapping components (Berridge & Robinson, 2003). These include motivation, RL and hedonic capacity (Admon & Pizzagalli, 2015), as well their interactions with specific cognitive and emotional processes. Moreover, anhedonia in depression seems to stem from an abnormal dopamine (DA) -dependent encoding of reward-related stimuli and RL, as well as motivation and reward-related decision making, more than experiencing pleasure per se (Pizzagalli, 2014; Treadway & Zald, 2011). Consistent with this dissociation, reward does not yield the normal responsiveness to "incentive salience" and subsequent behavioral adaptation in MDD (Henriques & Davidson, 2000). This behavioral insensitivity to reward has been linked to a poor integration of reinforcement history over time. Specifically, Pizzagalli et al. (2008; see also Vrieze et al., 2013) previously showed, using a probabilistic reward task, that MDD patients failed to develop a response bias towards more frequently rewarded stimuli or contingencies, in the absence of immediate reward delivery. Considering reward-based decision-making, Treadway

and colleagues (2012) elegantly showed that depressed patients were less willing to expend effort for gaining additional reward, compared to controls, highlighting a core deficit in reward anticipation and motivation in this mood disorder (see also Salamone & Correa, 2012).

RL provides a standard paradigm to explore the interplay of reward processing with motivation. It corresponds to the ability to extract, by trial and error, the value of actions (Sutton & Barto, 2018) and to approach reward-related feedback by means of specific motivational processes to eventually maximize reward. By virtue of these fundamental properties, RL allows to timely explore and characterize the nature and extent of reward-related deficits accompanying MDD (Pizzagalli, 2014). At the electrophysiological level, RL has been linked to specific DA-dependent event-related brain potentials (ERPs), including the error- and feedback-related negativity – ERN and FRN (Holroyd & Coles, 2002; Yeung, Holroyd, & Cohen, 2005). More specifically, reward prediction errors (RPE - either response-locked for ERN or feedback-locked for FRN) are thought to be generated in deep midbrain dopaminergic structures, which in turn release or inhibit the activation of the dorsal anterior cingulate cortex (Holroyd, Pakzad-Vaezi, & Krigolson, 2008; Proudfit, 2015; Ullsperger, Fischer, Nigbur, & Endrass, 2014). Interestingly, the ERN is usually overactive in internalizing psychopathology (Bakic, Jepma, De Raedt, & Pourtois, 2014; Endrass & Ullsperger, 2014; Frank, Woroch, & Curran, 2005; Koban & Pourtois, 2014; Olvet & Hajcak, 2009; Vaidyanathan, Nelson, & Patrick, 2012; Weinberg, Riesel, & Hajcak, 2012). Conversely the FRN, sometimes referred to as Reward Positivity (RewP), is usually blunted in MDD (Proudfit, 2015). A reduced FRN/RewP in depression could reflect a decreased reward sensitivity (Bress, Smith, Foti, Klein, & Hajcak, 2012; Weinberg & Shankman, 2016) as well as impaired ability to use the reinforcement history to drive implicit reward-based learning (Whitton et al., 2016).

Although the ERN and FRN/RewP have been extremely valuable to explore brain mechanisms of RL in the past (Eppinger, Kray, Mock, & Mecklinger, 2008; Holroyd & Coles, 2002), frontal-midline Theta oscillations (FMT, 4-8 Hz) have been put forward more recently as a complementary correlate of this process (Hajihosseini & Holroyd, 2013), bridging RPE signals with cognitive control implementation (Cavanagh, Figueroa, Cohen, & Frank, 2012; Cavanagh & Frank, 2014; Holroyd & Umemoto, 2016). FMT power increases during error and negative FB processing, as well as during response conflict and unexpected events in general (Cavanagh, Frank, Klein, & Allen, 2010; Cavanagh, Zambrano-Vazquez, & Allen, 2012; Cohen & Donner, 2013; Cohen, Wilmes, & van de Vijver, 2011; Gheza, De Raedt, Baeken, & Pourtois, 2018). During RL, it is thought to link prediction errors to behavioral adaptation and learning (Cavanagh et al., 2010; E. H. Smith et al., 2015; van de Vijver, Cohen, & Ridderinkhof, 2014; van de Vijver, Ridderinkhof, & Cohen, 2011), presumably by signaling the need for enhanced cognitive control (Cavanagh & Frank, 2014) as a function of the current prediction error. In the context of RL, cognitive control includes action selection or inhibition (response level) and working memory updating according to the accumulating action-outcome history (FB level; Barch et al., 2017; Collins et al., 2017). Unlike the ERN or FRN, FMT oscillatory perturbations arising from the ACC (Cohen, Ridderinkhof, Haupt, Elger, & Fell, 2008; Wang, 2005) reflect both phase-locked and non-phase-locked EEG activity, thereby providing a signal that is only partially captured by ERPs (e.g. the N200; Hajihosseini & Holroyd, 2013). In accordance with this notion, Cohen and Donner (2013) previously demonstrated that removing the phase-locked component of the EEG (i.e., the ERP) did not reduce the strength of the conflict-related modulation of the residual (non-phase locked – “induced”) FMT. Rather, during response conflict, the induced FMT showed stronger behavioral association with changes in response time. Moreover, compared to the ERP components, FMT may better

capture neural effects associated with long-distance connections between the medial and lateral prefrontal cortex (E. H. Smith et al., 2015). By virtue of these properties, assessing induced FMT during RL may provide novel insight into reward-based learning in depression, more closely related to hedonic capacity (i.e., propensity to modulate behavior as a function of reward), and beyond DA-dependent RPE detection.

Whereas FMT oscillations provides a useful electrophysiological correlate of performance monitoring during RL, yet MDD is also characterized by core motivational deficits. More specifically, MDD is accompanied by blunted approach-related motivation, while being sometimes associated with an excessive withdrawal/avoidance behavior concurrently. Noteworthy, older psychophysiological research carried out by Davidson and colleagues (Davidson, 1993, 1998a; Davidson, Ekman, Saron, Senulis, & Friesen, 1990; Henriques & Davidson, 2000) and extensively pursued over the last three decades (Coan & Allen, 2004; Davidson, 2004; Gotlib, Ranganath, & Rosenfeld, 1998; Eddie Harmon-Jones & Gable, 2017) showed that this approach-withdrawal motivation model explains a large amount of inter-individual variability in affect styles and emotional reactivity, and maps onto two competing brain systems in the frontal lobe, as expressed by hemispheric frontal asymmetries in the Alpha band, selectively. Alpha power contributing to frontal asymmetry effects is commonly reported from a set of homologous frontal leads along the coronal axis (in particular F8-F7, F6-F5, F4-F3 and F2-F1; see Stewart, Bismark, Towers, Coan, & Allen, 2010), and is thought to be generated mostly (but not only) from the proximal dorsolateral prefrontal cortex (dlPFC) (Pizzagalli, Sherwood, Henriques, & Davidson, 2005), even though a clear regional specificity remains difficult to establish. With regard to MDD, anhedonic symptoms such as loss of interest, reduced hedonic capacity and decline in goal-related motivation have been linked to a putative hypoactive approach-motivation system, as reflected by lower left prefrontal activity at rest (Davidson, 1998b; Henriques and Davidson,

1991; Nusslock et al., 2015; Pizzagalli et al., 2005; see Thibodeau et al., 2006 for a meta-analysis), and source-estimated in the precentral and midfrontal gyri (E. E. Smith, Cavanagh, & Allen, 2017). Although such a broad dichotomy of frontal lobes specialization might be too coarse (Miller, Crocker, Spielberg, Infantolino, & Heller, 2013), and a recent meta-analysis showed that traditional ways of assessing Alpha asymmetry have limited diagnostic value for MDD (van der Vinne, Vollebregt, van Putten, & Arns, 2017), recently important methodological advances has been put forward to increase the robustness and heuristic promise of this metric (E. E. Smith, Reznik, Stewart, & Allen, 2017). Moreover, individual differences in frontal asymmetry and their association to depression seems to be more pronounced during emotionally or motivationally evocative tasks (e.g. when approach motivation is manipulated and induced; Shankman et al., 2007; Stewart et al., 2014, 2011) rather than at rest, and thus may be more informative when conceived as a state response (i.e., "response capability"; Coan et al., 2006) as opposed to a trait characteristic. For instance, a recent study showed that approach motivation reflected by asymmetrical frontal cortex activation during reward anticipation distinguished depressed from never-depressed individuals, and was specifically associated with motivation-related symptoms (Nelson, Kessel, Klein, & Shankman, 2017).

In this study, we had the unique chance to assess, using behavioral and EEG methods, brain mechanisms of RL (using FMT oscillatory perturbations) as well as motivation (using frontal Alpha asymmetry) concurrently in a large cohort of treatment resistant MDD patients, and compare them to age/sex/education-matched healthy controls. To explore RL, we capitalized on a well-validated probabilistic learning task (Eppinger et al., 2008) previously used and validated in our laboratory (Bakic et al., 2017, 2014). In short, the added value of this task is that three reward probabilities are manipulated concurrently and their effects on the learning rate and on phasic signals of enhanced cognitive control can be explored

using appropriate EEG methods (van de Vijver et al., 2014). More specifically, learned stimulus-response associations should lead to increased FMT for incorrect responses and decreased FMT for negative FB. Based on the evidence reviewed above, we formulated the following hypotheses. (i) At the behavioral level, the learning slope should be steeper and accuracy higher for high compared to low reward probability, with a possible impairment of these RL-based effects in MDD patients. (ii) At the electrophysiological level, RL should be abnormal in MDD compared to controls, as evidenced by specific alterations in FMT oscillatory activity. In healthy controls, FMT should exhibit symmetric changes between response errors and negative FB as a function of reward probability (van de Vijver et al., 2014), but might be hypoactive in MDD patients, suggesting blunted cognitive control modulation during RL. However, we predicted that these group differences should likely depend on reward probability (i.e., strength of stimulus-response association), given that MDD might interfere with RL selectively when higher efforts and enhanced motivation are required to foster learning (Bakic et al., 2017; Salamone, Correa, Nunes, Randall, & Pardo, 2012; Thomsen, 2015; Treadway et al., 2012). In particular, we expected larger group differences at the FB level when reward probability was low compared to high because a higher motivation is presumably required in this condition for maintaining an active and sustained exploration of the FB. (iii) Core motivational processes should be impaired as well in these MDD patients. More specifically, we surmised that MDD patients, compared to the controls, would show hypo left relative to right frontal activation while processing the FB, reflecting a deficient approach-related motivation (Davidson, 1998b; Nelson et al., 2017).

3. Methods

3.1. Participants.

Forty-two patients diagnosed with unipolar MDD (30 females, mean age: 41.40, SD=12.04; meeting DSM-V criteria – American Psychiatric Association, 2013) and sixty HCs matched on group level for age, sex and education (35 females, mean age: 37.90, SD=12.82) participated in the current study. All participants had normal or corrected to normal vision. The MDD sample was recruited from ambulatory and hospitalized patients of the Ghent University hospital. This EEG study was part of a larger clinical trial (http://clinicaltrials.gov/show/NCT01832805) that examined beneficial effects of neurostimulation (accelerated intermittent theta burst stimulation - iTBS) of the left dorsolateral prefrontal cortex (dlPFC) in MDD (see also Duprat et al., 2016). The present EEG study included baseline data collected prior to the start of the treatment, and examined group level differences during RL between MDD patients and HCs at this specific time point only. The patients' diagnosis were confirmed by the Mini International Neuropsychiatric Interview (Sheehan et al., 1998). Depression severity was assessed by a certified psychiatrist with the 17-item Hamilton Rating Scale for Depression (HRSD; Hamilton, 1980), and the 21-item Beck Depression Inventory (BDI; Beck, Steer, & Brown, 1996). Hedonic responses were assessed with self-report questionnaires, the Snaith-Hamilton Pleasure Scale (SHAPS; Snaith et al., 1995) and the Temporal Experience of Pleasure Scale (TEPS; Gard, Gard, Kring, & John, 2006); the latter assessing anticipatory separately from consummatory Anhedonia. Importantly, these patients were deemed treatment resistant (Fava, 2003) and classified as at least Stage I treatment resistant (i.e., they had at least one unsuccessful treatment trial with an SSRI/SNRI; Rush, Thase, & Dubé, 2003). Moreover, all the patients underwent a washout period from medications and were medication-free at least two weeks before the baseline assessment. Only habitual benzodiazepine

agents were allowed[1]. Exclusion criteria were (I) bipolarity, (II) the use of antipsychotics, tricyclic antidepressant, (III) a history of neurological disorders including epilepsy and head injury with a loss of consciousness, (IV) a history of electroconvulsive therapy, (V) a past or present substance abuse, (VI) a past or present experience of psychotic episodes, and (VII) learning disorders. Some of those admitted to the study were further excluded a posteriori for the following reasons. (i) Insufficient or no learning during the main task, as indicated by learning curves below chance level (11 HCs, 6 MDDs). (ii) Excessively noisy EEG signal or severe EEG recording issues (3 HCs, 2 MDDs). (iii) Eight controls were excluded due to high or missing BDI scores. (iv) Four controls were excluded to match age and gender between HCs and MDD patients at baseline. This was achieved by removing the oldest HCs. The final sample consisted of 34 HCs (27 females, mean age: 36.21 years, SD=11.66) and 34 MDD patients (27 females, mean age: 42.68 years, SD=11.69). The study was approved by the ethics committee of the Ghent University Hospital.

3.2. Probabilistic learning task.

Participants performed a probabilistic learning task (Fig. 1) previously devised and validated by Eppinger et al. (2008) and used in Bakic et al. (2017, 2014). Colorful line drawings (Rossion & Pourtois, 2004) were used as visual stimuli, presented against a white homogenous background on a 17-inch computer screen. These stimuli consisted of visual objects

[1] Benzodiazepines were mostly prescribed as sleeping medication, and only in case of ongoing therapy. Possible influence of this medication on approach-motivation or RL is not documented. To note, clear frontal alpha asymmetry was previously reported in a sample of depressed patients under antidepressant medication, including lorazepam (Debener et al., 2000). Benzodiazepines administration might influence “liking” reactions, more than motivational aspects (“wanting”) of the reward system (Berridge, Robinson, & Aldridge, 2009).

belonging to different semantic categories (artifacts, buildings, musical instruments, clothes, vehicles, furniture). Their mean size was 7 cm width x 5 cm height, corresponding to 5 x 3.6 degrees of visual angle at 80 cm viewing distance. On each trial, participants were required to press either the response button “A” or “B” within 800 milliseconds after stimulus onset (i.e., two-alternative forced-choice discrimination task). They were instructed to infer and learn, by trial and error, different hidden stimulus-response (S-R) mappings. Feedback on the choice made was given following every response. In each of two consecutive task blocks (n=240 trials each) participants were presented with six different visual stimuli, belonging to three hidden conditions that differed regarding reward probability. In each block, two stimuli had a 100% “deterministic” S-R mapping. Two stimuli had a “probabilistic” 80% S-R mapping. Finally, in the “random” S-R mapping, the two stimuli were equally often associated to each of the two response keys. Each stimulus was presented 40 times. The two different blocks differed in terms of the six visual stimuli used to avoid learning across them. Trial order within a block, as well as order of the two blocks were alternated across participants. The trial structure was as follows: a fixation cross lasted for 250 ms, followed by a 250 ms blank screen. The stimulus was then presented for 500 ms, followed by a blank screen for 300 ms. The response time-window lasted for 800 ms following stimulus onset and was fixed (i.e., decisions made with response times shorter than 800 ms did not terminate the event). Five hundred milliseconds after response deadline a performance feedback was presented for 500ms. The feedback was provided in the form of a Dutch written word, appearing in black on a white homogenous background. The word was “goed” (correct), “fout” (incorrect), or “te traag” (too late). The inter trial interval was set constant (500 ms) and corresponded to a blank screen. Manual responses were recorded using a Cedrus response box. Prior to the testing session, HCs and MDD patients were asked not to consume any caffeine or nicotine for a period of at least 2 hours. In order

to get acquainted with the task, they completed a short practice session of 20 trials with an extra set of stimuli. The whole experiment lasted approximately 2 hours (see Bakic et al., 2017).

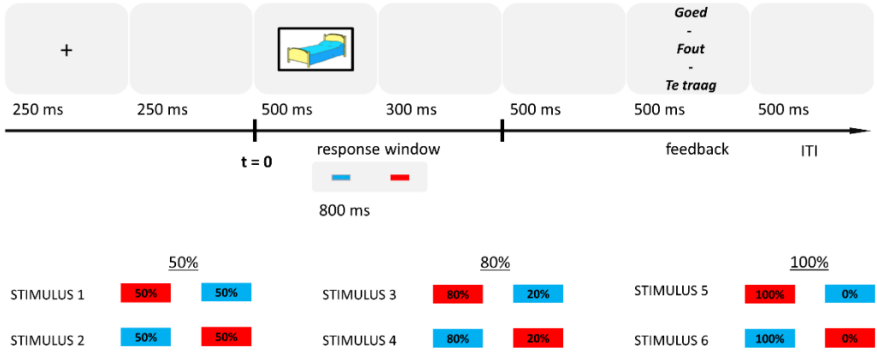


Figure 1. (Top) Trial structure. (Bottom) The experiment consisted of two consecutive task blocks, each including 6 different stimuli that were each repeated 40 times. On each and every trial, participants were asked to perform a two-alternative forced choice task (was the stimulus associated with response “A” or “B”?), within a 800 ms time limit. Unbeknown to them, these 6 stimuli were assigned to different reward probabilities (deterministic, probabilistic or random).

3.3. EEG data recording, reduction and statistical analyses.

3.3.1. EEG recording and preprocessing.

Continuous EEG was recorded during the task and sampled at 512 Hz using a BioSemi ActiveTwo system, with Common Mode Sense (CMS) active electrode and Driven Right Leg (DLR) passive electrode serving as ground for internal gain scaling (www.biosemi.com). A 64 channel cap, 4 peri-ocular electrodes (above and below left eye and on left and right cantus) and 2 electrodes on the mastoids were used. The EEG signal was referenced offline to the averaged mastoids and filtered offline with a high-

pass 0.5 Hz and low-pass 45 Hz FIR filters. All data processing was conducted in MATLAB (R2013b; The MathWorks Inc., Natick, MA) using EEGLAB (Delorme & Makeig, 2004) and custom scripts.

An independent component analysis was run on the continuous data. Individual epochs were then extracted around the response onset (-1.9 to 2.0 sec) and FB onset (-2.4 to 1.5 sec), and the pre time-locking event baseline was subtracted (-200 to 0). Artefactual ICA components were selected focusing on eye artifacts and spatial or temporal discontinuities, and were removed from both the FB-locked and response-locked datasets. A final dataset-wise rejection of residual epochs with artifacts was conducted by means of extreme values identification (±100μV cutoff, in a -1900 to 600 ms time window) and visual inspection. Trials containing late responses, absence of response or double response (both A and B button presses) were discarded from all analyses. For the probabilistic condition (80% feedback validity condition), trials containing unexpected feedback (i.e., 20% of trials with an inverted S-R mapping) were also removed (see Bakic et al., 2014). For each dataset (response or FB) clean epochs were grouped according to the six main conditions derived by crossing the factors “reward probability” (three levels) and “accuracy” (correct or incorrect response; positive or negative FB). In order to attenuate signal to noise ratio (SNR) differences between conditions, for each subject and dataset, conditions were balanced according to their average trial count: when a condition’s count exceeded this value, a subset of epochs corresponding to this average was randomly selected. The epochs retained were included in the following analyses (individual mean and SD across conditions and datasets: HCs = 52.1, 16.9; MDD = 48.8, 16.7. See Suppl. Table 1 for the condition-specific trial number).

3.3.2. Time frequency analysis.

The time-frequency decomposition was conducted using EEGLAB built-in std_ersp() function, based on complex Morlet wavelet convolution (1.6-9.85 cycles, 1.3-40 Hz, 75 log spaced frequencies, 200 time points), in which the complex power spectrum of the single-trial EEG time series (obtained from FFT) was multiplied by the complex power spectrum of a family of complex Morlet wavelets, and then the inverse Fourier transform was taken (Cohen, 2014; van de Vijver et al., 2014). After convolution of the wavelets with the EEG, power was defined as the modulus of the resulting complex signal. The convolution was performed separately on feedback-locked and response-locked data. Feedback-locked and response-locked power time series were epoch-wise normalized dividing by the pre-stimulus baseline power, and decibel (dB) converted (10*log10[power/baseline]). The baseline interval used for the normalization was defined within the pre-stimulus interval with a fixed range for feedback-locked epochs (-1700 to -1500 ms pre-FB, equal to -400 to -200 ms pre-stimulus) and a varying range for the response-locked epochs (-1100 to -900 ms pre-response, equal to around -650 to -450 ms pre-stimulus given an average response time of ~450 ms). The baseline for the response-locked epochs ensured that this range did not extend over -100 ms before the stimulus presentation, even when considering the longest possible response time (800 ms).

Time windows and channel location were based on the theta-band maximal power from the grand average of all conditions (see Fig. 2). Specifically, maximum values were reached at prefrontal scalp locations along the midline (Fz & FCz), in agreement with the existing RL and cognitive control literature (Cavanagh et al., 2010; Nigbur, Cohen, Ridderinkhof, & Stürmer, 2012; van de Vijver et al., 2014). As can be seen from Fig. 2a, FMT power increased before the response and extended until around 200 ms after it, while it peaked around 400 ms after the

feedback (see Fig. 2b). To note, previous studies on FMT and action monitoring showed that an early FMT power burst preceding the response onset is usually expressed for both correct and incorrect responses (this comparison is shown in Supplementary Fig. 1; see also Cavanagh, Cohen, & Allen, 2009; van de Vijver et al., 2014), while only incorrect responses elicit strong post-response FMT activity (see Fig. 2c). This pattern aligns well with the assumption that FMT reflects to some extent prediction error in case of response error. In line with these previous studies, FMT power was extracted in the 200ms time window following response onset.

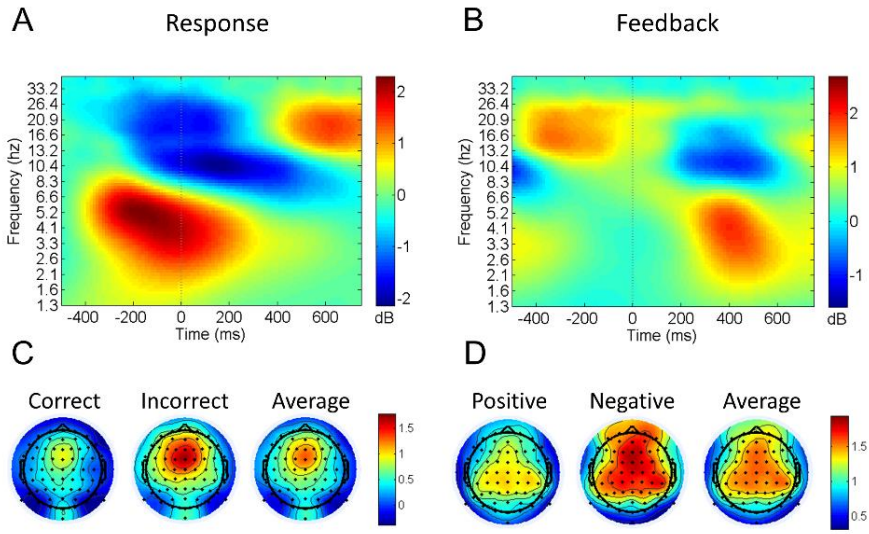


Figure 2. Induced power. (a) Time-frequency decomposition (whole spectrum) at electrodes Fz and FCz (combined) for HCs (average of all three reward probabilities and two accuracy conditions) when considering the response level, and revealing a clear increase in FMT power (3 to 7 Hz) peaking around 100 ms before response onset and extending till around 200 ms after it. (b) Same analysis performed when considering the FB, and showing a FMT power increase occurring 300 – 500ms after FB onset. This interval was used to extract FMT power for the FB. (c) Horizontal scalp topographies of FMT power for the response (0 – 200ms), showing a clear FMT increase (when collapsing the three reward probabilities) at prefrontal electrodes along the midline (Fz & FCz) for incorrect compared to correct responses. (d) Horizontal scalp topographies of FMT power for the FB (300 – 500ms), showing a clear

FMT increase (when collapsing the three reward probabilities) at prefrontal electrodes along the midline (Fz & FCz) for negative (incorrect) compared to positive (correct) feedback.

Oscillatory dynamics may be influenced by individual characteristics (i.e., age and clinical status). For this reason, we identified the frequency with maximal power for each subject in a window ranging 3.5 to 8 Hz, and from 300 to 500 ms after FB onset (from the channels Fz & FCz). Peak frequencies were close to the canonical Theta lower boundary (4 Hz) for the two groups alike (HC: mean = 4.20 Hz, SD = 0.94; MDD: mean = 4.21 Hz, SD = 0.98), thus we set the FMT frequency range from 3 to 7 Hz in all subsequent analyses, for both groups. For these reasons, FMT power changes (3-7 Hz) were defined as the mean computed within 0 to 200ms and 300 to 500ms after the response or FB respectively, and across channels Fz and FCz.

We further divided FMT power in the induced (non-phase-locked) and evoked (phase-locked) components in order to isolate oscillatory dynamics from time/frequency changes driven by ERPs. To this aim, we first computed the individual ERPs for each condition, time-locked to the response or the FB event; second, the conditional ERP was subtracted from each single EEG epoch belonging to the relative condition; third, the convolution and normalization procedure described above was repeated to obtain the induced FMT. The evoked power was derived by subtracting the induced from the total power (Cohen, 2014).

3.3.3. Frontal alpha-asymmetry.

All cleaned FB-locked epochs were included in this analysis, merging reward probability and accuracy factors. Whereas frontal alpha asymmetry is often computed using resting state EEG recordings, here we analyzed it using active task data because it has been shown that emotionally or

motivationally relevant states may produce more robust individual differences than resting state data (i.e., response capability model, see Allen & Reznik, 2015; Coan et al., 2006). Using this framework, MDD impairments in approach-motivation may emerge as a lateralized state response while approaching the FB. The segmented EEG data were converted to the scalp Laplacian (Kayser & Tenke, 2006), a reference-free current sources density estimation, to increase spatial selectivity and to minimize volume conduction. Since the Laplacian attenuates the contribution of distal volume-conducted sources (e.g. the occipital cortex and deep sources), it highlights the contribution of local electrode activities and radial dipoles (Perrin, Pernier, Bertrand, & Echallier, 1989; E. E. Smith, Reznik, et al., 2017), thus improving the topographical localization of surface EEG signals. We computed the power spectral density (PSD) applying a fast Fourier transform (FFT) on the task data (spectopo() function), obtaining a dB converted estimation of relative power in a range of frequencies, with unit 10*log10(uV2/Hz). The FFT transform was applied to each epoch in a single one-second segment (-100 to 900 ms relative to the FB) weighted with a Hamming window (512 point window length given a sampling rate of 512 Hz). The resulting PSD values were then averaged across epochs, for each subject and channel. Alpha power was defined as the average in the 8-13 Hz range.

We further adopted a stringent standardization procedure that controls for individual variability in the band-power estimation. For each subject, normalized single-site Alpha power values were computed by dividing the power at each channel by the summed power across all channels; then, these ratios were transformed in Z scores, normalizing over all electrodes (E. E. Smith, Reznik, et al., 2017). This procedure allows to control for individual nuisance variable such as scalp thickness and overall global power, providing a metric suited for exploring each homologous site's contribution to the lateralization, as well as correlations with criterion variables (e.g. clinical scales).

3.3.4. Statistical analyses.

At the behavioral level, learning was expressed as percentage of correct responses varying as a function of time, using four consecutive bins of trials (see Bakic et al., 2017). We compared the learning performance between MDD patients and HCs by means of a mixed-design ANOVA with reward probability and bin as within-subject factors, and group as between-subject factor. We also analyzed the effects of group and reward probability on reaction times (RT) for correct responses, as well as the amount of "too late" responses, by means of mixed-design ANOVAs.

At the electrophysiological level, we analyzed FMT power changes at the response and FB levels separately, and we compared MDD patients to HCs by means of a mixed-design ANOVA with accuracy and reward probability as within-subject factor, and group as between-subjects factor. Follow-up statistical analyses on the evolution of FMT power across successive trials were performed using Bayesian Multilevel Models (BMLM), implemented in R (R Core Team, 2017) with the "brms" package (Bürkner, 2017; Nalborczyk, Batailler, Loevenbruck, Vilain, & Bürkner, in press).

Alpha asymmetry was assessed considering the normalized Alpha power at typical frontal sites (F4 & F3). We included in the analysis parietal sites (P4 & P3) in order to establish the specificity of the effect for the frontal region. We compared frontal Alpha asymmetry for MDD patients to HC by means of a mixed-design ANOVA with region (frontal or parietal) and hemisphere (right or left) as within-subject factor and group as between-subjects factor. In order to assess the spatial localization of the frontal alpha asymmetry effect found with the first analysis, we performed a second analysis where we used an extended array of frontal homologous pairs (F2 & F1, F4 & F3, F6 & F5, F8 & F7). For this analysis, we used a mixed-design ANOVA with pair and hemisphere as within-

subject factor and group as between-subjects factor. Last, we assessed the reliability of task-related Alpha asymmetry by means of split-half correlations. For either the HC or MDD group, we split the dataset according to odd and even trials (accuracy and probability conditions being balanced) and computed asymmetry scores between a set of frontal and parietal sites (F2-F1, F4-F3, F6-F5, F8-F7, P4-P3). Based on the raw Alpha power (without normalization), the asymmetry score was defined as the difference between the right-site and the left-site PSD (i.e., 10*log10[Right] – 10*log10[Left]), with higher values on this index putatively reflecting relatively greater left activity (i.e., relatively greater right alpha). Pearson's product-moment correlation coefficients were calculated between asymmetry scores derived by either odd or even trials, for each location and group.

For all the analyses, the Greenhouse-Geisser procedure was adopted to correct the degrees of freedom when the sphericity was violated. For post-hoc pairwise comparisons, a Bonferroni correction was used.

4. Results

4.1. Clinical and behavioral data.

As can be seen from Table 1, MDD patients had significantly higher depression scores (on all scales used) than HCs at baseline. Behavioral task data confirmed that for HCs, learning was influenced by time and reward probability, as expected (Bakic et al., 2014; Eppinger et al., 2008). More specifically, learning was steep and the highest for the deterministic condition, intermediate for the probabilistic condition and absent for the random one. MDD patients exhibited the same learning profile (see Fig. 3). Comparing MDD patients with HCs, the ANOVA failed to evidence a significant group x reward probability x bin [$F(4.59,303.21) = 0.327$, $p = .883$, $\eta 2p = .005$] or group x reward probability interaction [$F(2,132) = 0.297$, $p = .744$, $\eta 2p = .004$], or main effect of group [$F(1,66) = 0.771$, $p = .383$, $\eta 2p = .012$], whereas the reward probability x bin interaction was highly significant [$F(4.59,303.21) = 29.229$, $p < .001$, $\eta 2p = .307$] and unambiguously translated improved behavioral performance across time when reward probability increased, for both groups. The analysis for RT speed showed significant main effects of group [$F(1,66) = 6.632$, $p = .012$, $\eta 2p = .091$] and of reward probability [$F(2,132) = 7.511$, $p < .001$, $\eta 2p = .102$], indicating overall slower responses for MDD patients than HCs, as well as faster RTs when reward probability increased (see Fig. 3B). For each condition, the number of “too late” responses was modest, yet larger for MDD patients (mean = 4.10, SE = 0.36) than HCs (mean = 2.96, SE = 0.24) [$F(1,66) = 6.971$, $p = .010$, $\eta 2p = .096$], and varied across the three reward probability conditions [$F(1.83,121.06) = 7.981$, $p < .001$, $\eta 2p = .106$], increasing when reward probability decreased. We also used computational modeling to extract alternative indices of learning, including the learning rate and an exploration parameter (Jepma & Nieuwenhuis, 2011), but failed to observe group differences for them. A significant lower amount of switches after negative FB for MDD patients compared to HCs

was observed only during the second part of the experiment (bins 3 and 4; see Bakic et al., 2017 for details regarding these analyses).

	HC	MDD	t
Number	34	34	
Gender (F/M)	27/7	27/7	
Age	36,21 (11,66)	42,68 (11,69)	-2,29*
BDI_II	4,26 (4,39)	31,81 (9,23)	-15,63**
Anhedonia	0,76 (1,05)	5,13 (2,15)	-10,57**
HAM_D	1,18 (2,04)	21,47 (5,29)	-20,87**
SHAPS	0,59 (2,41)	7,21 (4,10)	-8,11**
TEPS	79,12 (8,34)	59,45 (13,22)	7,34**
Consumatory	37,62 (5,11)	29,37 (7,37)	5,36**
Anticipatory	41,50 (5,63)	30,08 (7,47)	7,12**

*p<.05, **p<.01

Table 1. Demographic and clinical data for HCs and MDD patients (means are provided together with the standard deviations in parenthesis). Independent samples t-tests for BDI II (df = 64), Anhedonia subscale of BDI II (df = 64), HAM D (df = 66), SHAPS (df = 66) and TEPS (df = 66), with the corresponding subscales (dfs = 66). Note that due to some missing data, the degrees of freedom (df) were different for the BDI II scale.

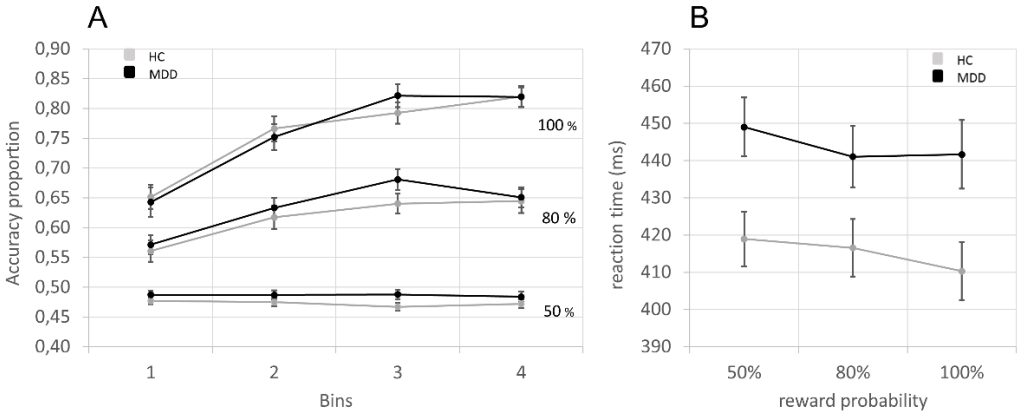


Figure 3. Behavioral results. (a) Accuracy data (i.e., proportion of correct responses) decomposed as a function of bin, condition and group. Each bin corresponds to the average of 40 trials (20 consecutive trials per condition for each of the two task blocks). (b) Response latencies (for correct responses) decomposed as a function of group and reward probability. The error bar corresponds to 1 standard error of the mean.

4.2. Fronto-Midline Theta.

As can be seen from Fig. 4, most of the total FMT power reflected the modulation of ongoing theta-band oscillations that occurred during the response or the FB but was not phase-locked to them (i.e., induced). Thus, we focused our analyses on the induced FMT only, that is the time-frequency representation in the Theta band of EEG dynamics that are task-related (i.e., relative to the pre-stimulus baseline) but do not contribute to ERPs[2].

[2] The choice of analyzing the induced component of FMT was not motivated by a different physiological interpretation for the induced vs. evoked component of the signal (see Donner and Siegel, 2011; Gray and Singer, 1989; Tallon-Baudry and Bertrand, 1999). Rather, it was based on a previous EEG study linking the induced FMT to behavioral adaptation (Cohen & Donner, 2013), as well as our goal to supplement the standard ERP data analysis (presented elsewhere, see Bakic et al., 2017) with time-frequency decompositions for which the specific contribution of the evoked/ERP component was removed.

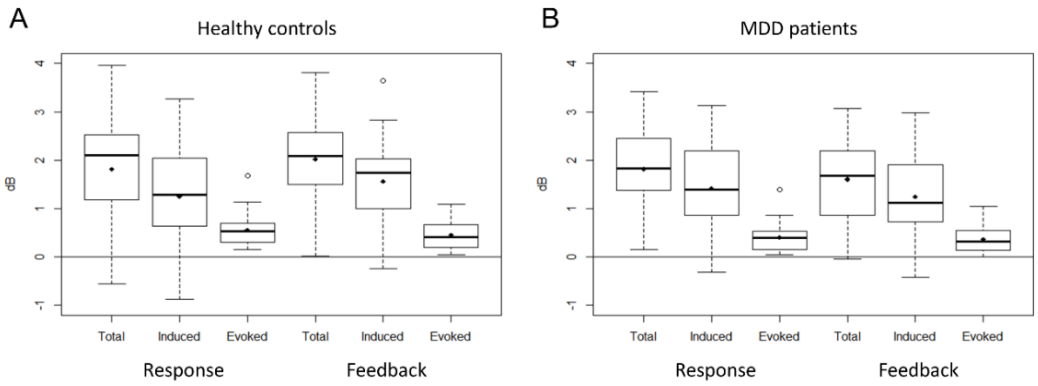


Figure 4. (a) Boxplot analysis showing for each level separately (either response or FB), the proportion of total, induced and evoked FMT power changes for HCs. These FMT power changes correspond to the average of the two response accuracies and three probability conditions. The bold horizontal line represents the median, the box represents the interquartile range, and the whiskers extend to the last data point within 1.5 times the interquartile range. Additional solid black symbols indicate the mean. This analysis shows that irrespective of the level considered, the induced (non-phase-locked) component of FMT accounted for most of the total FMT. By comparison, the evoked FMT (phase-locked – captured by ERPs) reflected a much smaller portion. This difference indicates a larger contribution of non-phase-locked than phase-locked responses (ERPs) to FMT power after both response and FB. (b) The same pattern was seen in MDD patients.

Induced FMT oscillatory activity was analyzed separately at the response and FB levels to ascertain that reward probability influenced these two levels in opposite directions. Importantly, we assessed whether abnormal RL in MDD patients was evidenced by systematic changes in FMT power, depending on reward probability and the level at which this information was processed (either response or feedback level). More specifically, we expected a larger group difference at the FB level when reward probability was low compared to high, due to a deficient sustained exploration of the FB in MDD. At the response level, the main effect of reward-probability was significant [$F(2,132) = 3.40$, $p = .036$, $\eta 2p = .049$], as well as the main effect of accuracy [$F(1,66) = 26.42$, $p < .001$, $\eta 2p =$

.286]. These main effects were accounted for by a monotonic decrease of FMT power as a function of decreasing reward-probability, and by higher power for incorrect compared to correct responses, for the two groups alike (see Fig. 6A). Moreover, reward probability interacted with accuracy [$F(2,132) = 10.74$, $p < .001$, $\eta2p = .140$], indicating that the monotonic power decrease along decreasing probabilities was evidenced for incorrect responses only [linear contrast: $F(1,66) = 21.04$, $p < .001$, $\eta2p = .242$]. For correct responses, FMT power followed the opposite trend [linear contrast: $F(1,66) = 4.00$, $p = .050$, $\eta2p = .057$]. In addition, FMT power differed between correct and incorrect responses only for the probabilistic (80%) [$F(1,66) = 9,41$, $p = .003$, $\eta2p = .125$] and deterministic (100%) [$F(1,66) = 35,60$, $p < .001$, $\eta2p = .350$] conditions, while this difference was not significant for the random (50%) condition [$F(1,66) = 0,19$, $p = .663$, $\eta2p = .072$]. Interestingly, this analysis also showed a significant interaction between group and accuracy [$F(1,66) = 6.35$, $p = .014$, $\eta2p = .088$], indicating a clearer separation between correct and incorrect responses for HCs [$F(1,66) = 29.34$, $p < .001$, $\eta2p = .308$] than MDD patients [$F(1,66) = 3.43$, $p = .068$, $\eta2p = .049$], who in turn showed a trend for stronger FMT power after correct responses, compared to HCs [$F(1,66) = 3.38$, $p = .070$, $\eta2p = .049$]. The main effect of group [$F(1,66) = 0.46$, $p = .500$, $\eta2p = .007$], interaction between group and reward probability [$F(2,132) = 0.09$, $p = .918$, $\eta2p = .001$], or the three way interaction [$F(2,132) = 0.42$, $p = .659$, $\eta2p = .006$] were all non-significant. At the feedback level, the ANOVA showed significant main effects of accuracy [$F(1,66) = 18.79$, $p < .001$, $\eta2p = .222$], and reward-probability [$F(1.83,120.99) = 11.06$, $p < .001$, $\eta2p = .144$]. Negative FB elicited stronger FMT power than positive one, while a symmetric effect of reward probability (relative to the response level) was found: FMT power monotonically increased with decreasing reward-probability (Figs. 5-6). Unlike what we found at the response level, we did not observe a significant interaction between accuracy and reward probability

[F(1.74,115.02) = 0.01, p = .989, η2p = .000] or between accuracy and group [F(1,66) = 1.13, p = .292, η2p = .017] at the feedback level. The main effect of Group approached significance [F(1,66) = 2.82, p = .098, η2p = .041], reflecting a trend for a generally reduced FMT power across all conditions in MDD patients compared to HCs. Likewise, the interaction between group and reward probability was trend significant only [F(1.83,120.99) = 2.37, p = .102, η2p = .035]. The three way interaction was not significant [F(1.74,115.02) = 0.87, p = .407, η2p = .013].

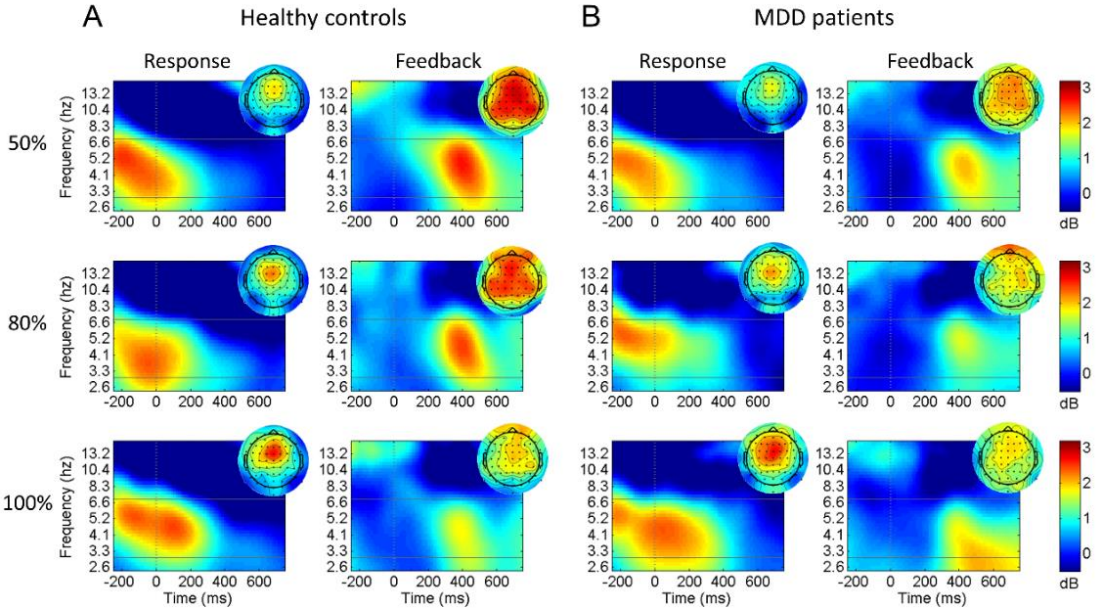


Figure 5. (a) FMT (3 to 7 Hz) power at electrodes Fz and FCz (combined) for HCs (n=34), separately for incorrect response (0 – 200 ms after its onset) and negative feedback (300 – 500 ms after its onset), and for each reward probability apart. Superimposed on each plot, the corresponding horizontal scalp topography is presented. (b) Same analysis for MDD patients (n=34). For both groups, FMT power varied with reward probability, but in opposing directions for incorrect response and negative FB: it increased with increasing reward probability at the response level while showing the opposite effect at the FB level. At the FB level, FMT power was reduced for MDD patients compared to HCs, especially for the low reward probability condition.

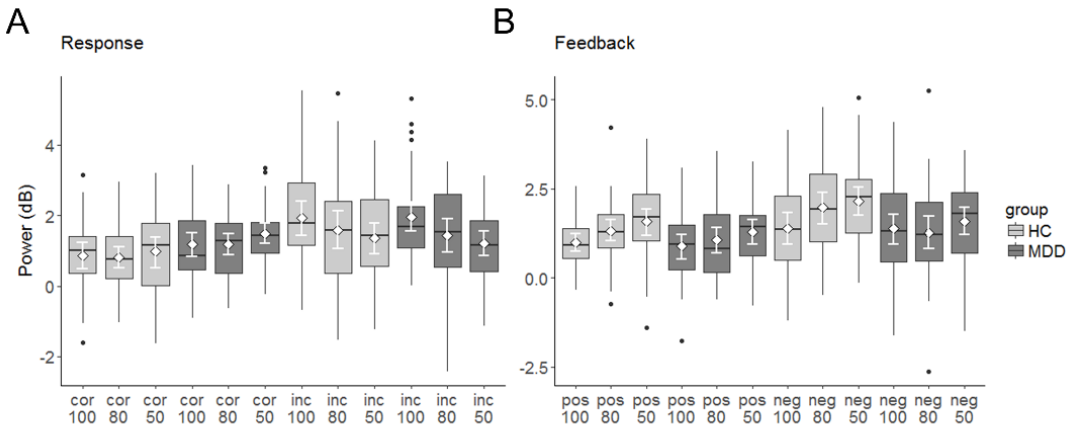


Figure 6. The boxplots show FMT power (3 to 7 Hz) recorded at electrodes Fz and FCz (combined) separately for the response (a) and the FB (b) levels, and for each accuracy level and reward probability. The two groups are coded with different shades of grey. The horizontal line represents the median, the box represents the interquartile range, and the whiskers extend to the last data point within 1,5 times the interquartile range. The black points indicate the outliers. Superimposed in white, the diamond symbols indicate the mean and the extending ranges cover the 95% confidence intervals.

In order to assess whether MDD patients showed a drop in motivation to decipher the most complex S-R associations (random condition) based on the feedback information, as the trend significant interaction between group and reward probability indirectly suggested (see above), we performed a follow-up analysis where we extracted FMT power changes at the single trial level (random condition) and modelled their evolution across successive trials. We reasoned that if MDD patients showed a drop in motivation, then FMT power should decrease in a steeper manner across trials for them in this condition, relative to the HCs. Relying on a Bayesian multilevel model analysis, we assessed the amount of evidence in favor of this specific hypothesis. The methodological and statistical details of this single-trial analysis are provided in the Supplementary Materials section. Figure 7A shows the outcome of this analysis, and is based on the model that best fit the observed data. This model included

the main effects of time, accuracy, group, and their interactions (see Supplementary Materials). Based on this model, we examined the difference between the probability distributions of the conditions of interest. Statistical results showed that for positive FB, the hypothesis of a steeper decrease of FMT power across time for MDD patients than HCs was 4.1 times more likely than the alternative one, predicting an opposite effect. For negative FB, results showed that it was 34.7 times more likely that FMT power decreased across trials more sharply for MDD patients than HCs, as compared to the opposite hypothesis. Last, the hypothesis that the group difference in the steepness of the slope was larger for negative than positive FB was 3.2 times more likely than the opposite one. Thus, this single trial analysis provided strong evidence in favor of the hypothesis that FMT power for negative FB decreased more sharply across trials for MDD patients than HCs, as well as some evidence that this effect was larger for negative compared to positive FB.

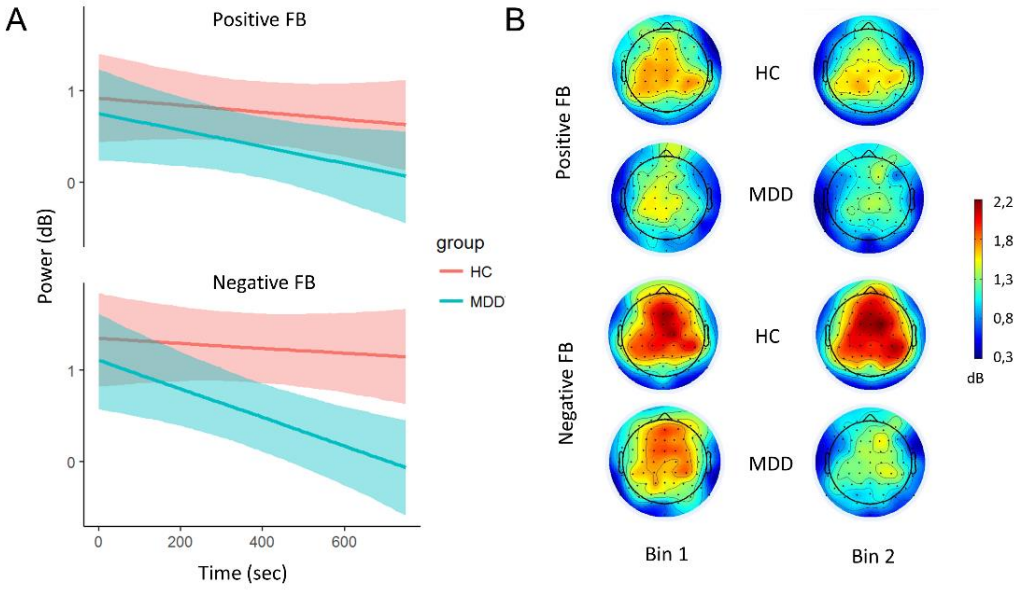


Figure 7. Temporal evolution of FMT power (FB level) across consecutive trials, for the 50% (random) probability condition. (a) Results of the Bayesian multilevel modeling. The figure represents the population-level marginal effects of the predictors time, accuracy and group on the estimated FMT power. These estimates are based on the model that best fit the observed data (see Supplementary Materials). The lines represent the mean of posterior probability samples at each second from the beginning of the task blocks, and for each condition. The shading represent the 95% credible interval around them. (b) For a comparison to the observed data, the horizontal scalp topographies show FMT power for the FB (300 – 500ms), for each accuracy level and group. In order to roughly represent the effect of time, FMT power was computed separately for the first and second bin of trials, considering all trials available for each subject. This was done for each block separately, before FMT power for the two blocks was collapsed.

4.3. Frontal Alpha-asymmetry.

To examine possible anomalies in approach motivation in MDD patients, we compared frontal alpha asymmetry (feedback level) between them and HCs. The ANOVA comparing frontal and parietal normalized Alpha power showed a significant two way interaction between hemisphere and group [$F(1,66) = 4.90$, $p = .030$, $\eta 2p = .069$]. Post-hoc comparison revealed a significant effect of hemisphere for the MDD group only [$F(1,66) = 4.84$, $p = .031$, $\eta 2p = .068$] translating a negative Alpha asymmetry index (left: mean = 0.103, SE = 0.145; right: mean = -0.316, SE = 0.105). Importantly, this effect was also qualified by a significant interaction with region [$F(1,66) = 4.63$, $p = .035$, $\eta 2p = .066$]. Post-hoc comparisons revealed a significant effect of hemisphere for frontal sites in the MDD group exclusively $F(1,66) = 5.56$, $p = .021$, $\eta 2p = .078$], expressed as a negative asymmetry index (corresponding to relatively higher left than right alpha power, thus translating a relatively lower left than right frontal activation; left: mean = 0.343, SE = 0.220; right: mean = -0.345, SE = 0.163) (see Fig. 8). With regard to the HC group, the effect of hemisphere did not reach significance, although showed the opposite trend at the frontal region (left mean = -0.133, SE = 0.220, right mean = 0.260, SE = 0.163).

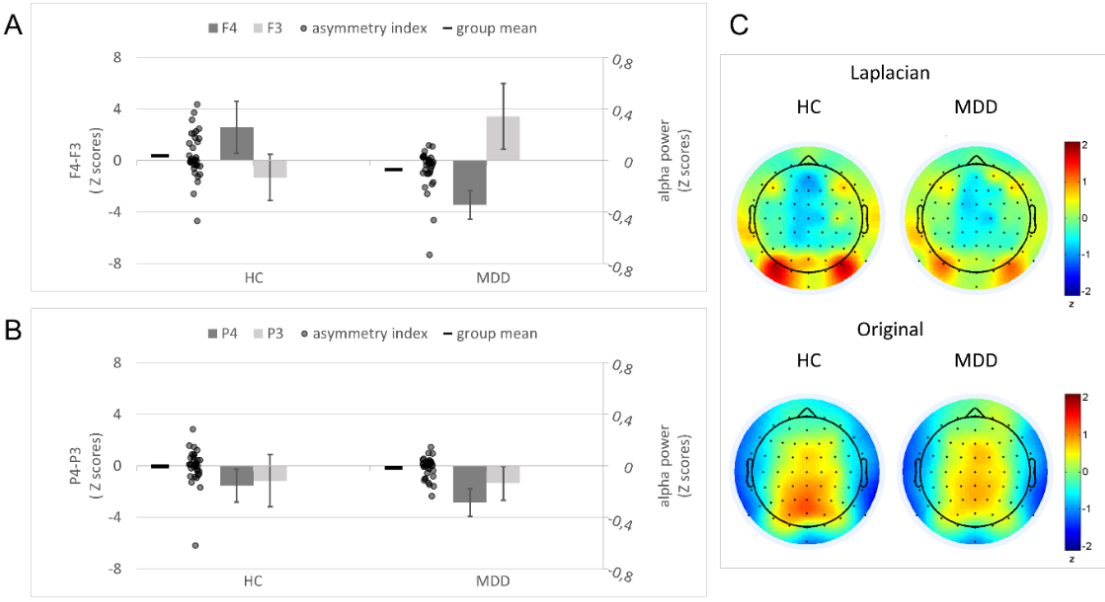


Figure 8. (a) Frontal alpha asymmetry results, separately for HCs and MDD patients. (b) Parietal alpha asymmetry results, for comparison purposes. Histograms represent mean alpha power for left (F3, P3) and right (F4, P4) channels, while the horizontal line bar reflects the mean asymmetry score (for each group) computed as the right- minus left- channel difference. The dots represent the subject-specific asymmetry scores. The error bar corresponds to 1 standard error of the mean. Note that both asymmetry scores and the alpha power at single channels refer to alpha power (with original unit 10*log10(uV2/Hz)) converted to Z scores by means of a within-subject topographical normalization. (c) Horizontal scalp topographies of alpha power (z scores), separately for HCs and MDD patients, computed on the Laplacian-filtered data (top) and the non-filtered data (bottom).

Moreover, in an additional analysis we considered an extended array of frontal electrodes on both sides (F2 & F1, F4 & F3, F6 & F5, F8 & F7) to assess whether frontal alpha asymmetry was circumscribed to a few isolated locations. The ANOVA comparing normalized Alpha power across frontal pairs showed a significant main effect of pair [$F(2.29,150.90) = 50.79$, $p < .001$, $\eta 2p = .435$]. This main effect was accounted for by a linear increase of Alpha power from medial to lateral pairs [$F(1,66) = 94.21$, $p < .001$, $\eta 2p = .588$]. Interestingly, the ANOVA showed also a significant

three-way interaction between pair, hemisphere and group [$F(2.01,132.51) = 4.43$, $p = .014$, $\eta 2p = .063$]. Post-hoc comparison revealed a significant effect of hemisphere in the MDD group and for the second pair selectively (F4 & F3; F4: mean = -0.345, SE = 0.163; F3: mean = 0.343, SE = 0.220; [$F(1,66) = 5.56$, $p = .021$, $\eta 2p = .078$]).

Finally, the split-half correlations indicated a strong reliability of Alpha asymmetry, translating a stable topographic distribution of Alpha power across different trials. For each site considered (F2-F1, F4-F3, F6-F5, F8-F7, P4-P3), the Alpha asymmetry score was highly correlated between odd and even trials, for both groups (HC range: $r = .987 – .997$, $N = 34$; MDD range: $r = .933 – .995$, $N = 34$).

Last, we also performed exploratory correlation analyses between the symptomatology or severity of depression and these electrophysiological measures, as well as between FMT and frontal Alpha power (see Supplementary Materials).

5. Discussion

Previous research in behavioral neuroscience, neuroimaging and psychiatry demonstrated that dysfunctions in fronto-striatal reward systems (i.e., Anhedonia, in combination with exaggerated stress responsiveness) play a central role in the etiology and maintenance of MDD (for a review, see Pizzagalli, 2014). Besides strong impairments in reward sensitivity (Bress et al., 2012; Foti, Carlson, Sauder, & Proudfit, 2014; Weinberg, Liu, Hajcak, & Shankman, 2015), abnormal reward anticipation and motivation are cardinal features of anhedonia in MDD (i.e., "wanting", Berridge & Robinson, 2003; Thomsen, 2015; Treadway & Zald, 2011), which in turn undermine the possibility to optimize behavior (learning) as a function of reward in these patients (Pizzagalli et al., 2008; Vrieze et al., 2013; Whitton et al., 2016). Such impairments should be visible during RL, where learning performance critically depends on the use, evaluation and exploration of specific incentives. In the present study, we sought to lend additional support to this dominant framework by comparing the neurophysiological correlates of RL and approach-related motivation between MDD patients and matched HCs. To this aim, we tested a large cohort of treatment resistant MDD patients (enrolled in a treatment study, see Duprat et al., 2016), and compared them to healthy, matched controls on a standard probabilistic learning task (Eppinger et al., 2008). We explored systematic changes of FMT oscillations as a function of reward probability, separately for the response (internal monitoring) and feedback level (external monitoring). FMT provides a reliable electrophysiological correlate of performance monitoring, putatively mediating the impact of RPE on behavioral adaptation and learning (Cavanagh et al., 2010; Cohen et al., 2008, 2011; E. H. Smith et al., 2015; van de Vijver et al., 2014). Interestingly, FMT has been proposed to signal the amount of control to be allocated over performance during extended and cognitive demanding tasks (Holroyd & Umemoto, 2016), but very few studies to date have evaluated systematically whether MDD could

influence it during RL (Cavanagh, Bismark, Frank, & Allen, 2011)[3]. Moreover, to examine possible group differences in approach motivation, we also extracted hemispheric frontal alpha asymmetry, measured throughout the task as a state response and using the most recent methodological recommendations for this metric, including Laplacian transformation and a stringent normalization procedure (Allen & Reznik, 2015; E. E. Smith, Reznik, et al., 2017; Stewart et al., 2014).

The present results do not support the assumption that anhedonia in MDD entails impaired RL, since we failed to observe clear-cut deficits in RL at the behavioral and EEG (FMT) levels in a large sample of MDD patients characterized by high levels of anhedonia. However, these results show that MDD and anhedonia are accompanied by deficits in approach motivation, as suggested by frontal alpha asymmetry as well as by a steep FMT power decrease across successive trials when considering the most challenging RL condition. In fact, despite being classified as at least stage I treatment resistant (Fava, 2003) and showing a high depression's severity as well as clear Anhedonia (both consummatory and anticipatory, see Table 1), these patients actually showed globally spared RL processes (see Fig. 3a). Learning was titrated at the behavioral level using either standard accuracy measures (Bakic et al., 2014; Eppinger et al., 2008), or alternative indices deriving from computational modeling, such as learning rate or exploration (see Bakic et al., 2017). The two groups

[3] Other studies already used in the past advanced time/frequency methods to evaluate FB processing in healthy and clinical populations, yet focusing on the phase-locked component of the EEG signal mostly (i.e., extracting power changes in specific bands after epochs averaging) in an attempt to parse the differential contribution of overlapping ERP components to the ERP power spectrum (Bernat, Nelson, & Baskin-Sommers, 2015; Bernat, Nelson, Steele, Gehring, & Patrick, 2011; Foti, Weinberg, Bernat, & Proudfit, 2015). Here, we used a very different approach and data analysis, where we purposely removed the ERP activity from the original EEG signal and used a time-frequency decomposition performed at the single trial level (Cohen, 2014; Cohen & Donner, 2013) with the aim to explore the contribution of non-phase-locked activity to power changes (in the theta band) as a function of reward probability and MDD.

showed comparable RL-based effects for these different measures. The only exception was the rate of switches after negative FB, which was significantly lower for these MDD patients compared to the HCs during the second part of the experiment (bins 3 and 4), selectively (see Bakic et al., 2017). This result suggested indirectly a possible drop in motivation and exploration across time in these MDD patients.

At the EEG level, FMT power was higher for incorrect than correct responses, and for negative than positive FB, as previously reported (Cavanagh, Figueroa, et al., 2012; Cavanagh et al., 2010; van de Vijver et al., 2014). As expected (van de Vijver et al., 2014), FMT power modulation strongly depended on reward probability, and was symmetrical between incorrect responses and negative FB (see Figs. 5-6). When the S-R was deterministic, FMT power was the largest for incorrect response. Conversely, when the S-R was random, FMT power was the largest for negative FB, confirming the sensitivity of this neurophysiological signal to reward-based learning. This neurophysiological effect aligns with the behavioral results showing that RL varied with reward probability. When learning was easy (deterministic S-R association), participants likely processed response errors at the response level on most trials, without the need to rely on the subsequent feedback to infer accuracy. By comparison, when it was hard or even impossible (probabilistic and random S-R associations, respectively), participants had to use actively the evaluative FB in order to infer accuracy, while evidence accumulated at the response level was probably too weak or absent. Hence, the corresponding effects on FMT power captured prediction errors and/or enhanced cognitive control in accordance with RL dynamics. Interestingly, only response errors, but not correct responses, elicited a large FMT power that decreased systematically with decreasing reward probability. At the FB level, both positive and negative FB showed a symmetric pattern compared to the response level, suggesting that FMT may reflect an unsigned prediction error signal. In fact, according to some authors

(Cavanagh, Figueroa, et al., 2012; Hajihosseini & Holroyd, 2013), FMT cannot reflect an axiomatic RPE coded by dopamine neurons because it does not show an interactive effect between reward and expectancy (see Caplin and Dean, 2008). Rather, it is mainly modulated by the (un)predictability of events in general, and it could reflect the amount of effort or control to be exerted as a result (output) of information processed by the ACC (including RPE signals), where the subjective value of the task might be estimated (Holroyd and Umemoto, 2016; see also Smith et al., 2015). In this scenario, the symmetric change in FMT power seen in our study between the response and FB levels across the three reward probability conditions could be explained by explicit predictions about performance (model-based reward learning; Dayan & Berridge, 2014), being initially made and eventually violated: if the S-R association was deterministic, on most trials a positive prediction could readily be computed at the response level, and be violated in case of response error. Instead, if the S-R association was probabilistic or random, the evaluative FB provided after the choice was respectively the main or only cue to gauge violations of prediction (in either direction).

Intriguingly, these effects were generally spared in MDD, disconfirming one of our main hypotheses. However, FMT power was slightly different between the two groups. At the response level, MDD patients showed only smaller differences in FMT power between correct and incorrect responses compared to HCs (Fig 6A. See also Suppl. Fig. 1). Specifically, compared to HCs, MDD patients showed an overall increase of FMT for correct responses, which may translate increased uncertainty at the response level (i.e., increased response conflict). When considering the FB level, both HCs and MDDs showed a symmetric pattern in FMT power modulation as a function of reward probability relative to the response level. Interestingly, MDD patients showed a numerically blunted FMT power modulation at the FB level, especially when reward probability was low (and hence the hidden S-R mapping was

hard to discover), although we failed to evidence a significant interaction effect between group and reward probability. Crucially, robust evidence for a group difference in this condition was provided by a follow-up analysis where we could model the evolution of FMT power across successive trials. As shown in Fig. 7, this group difference was expressed at the FB level in terms of a steeper decrease (slope) of FMT power as a function of time for MDD patients compared to HCs, and not simply as impaired discrimination of the evaluative FB as being positive or negative (i.e., both groups showed a different intercept at time 0; see also Suppl. Fig. 5). Further, this decrease of FMT power across successive trials was larger for negative compared to positive FB. These results suggest that both groups showed strong FMT power activity at the beginning of the task, but unlike MDD patients, HCs maintained enhanced cognitive control across time in response to FB, despite its low reward value in this condition. To note, in this condition learning was made impossible by design. Consequently, this drop shown by MDD patients at the neurophysiological level could not be accompanied by an impaired behavioral performance, relative to the HCs. As such, these FMT results corroborate to some degree the assumption that MDD likely interferes with specific motivation processes active during reward-based learning, as if it impaired selectively the involvement of extra efforts or resources necessary to yield learning in a complex situation where stimuli and responses carry low reward values (Pizzagalli et al., 2005; Salamone, Correa, Farrar, & Mingote, 2007; Thomsen, 2015; Treadway et al., 2012).

When considering specific motivation processes reflected by frontal Alpha asymmetry (as measured throughout the task as a state response to the FB; see Fig. 8), the results were clearer and showed a negative frontal Alpha asymmetry for MDD patients only, when considering the F3-F4 pair selectively. This asymmetry was expressed by positive normalized Alpha power for the left frontal site (F3), but negative Alpha power for the right frontal site (F4), relative to the average Alpha activity measured

across the entire scalp. By comparison, HCs did not show this asymmetry, but actually an opposite pattern. This clear group difference in lateralized frontal activity is consistent with the assumption of abnormal approach-related motivation in MDD (Eddie Harmon-Jones & Gable, 2017; Nelson et al., 2017; Pizzagalli et al., 2005), here expressed as a motivational disengagement during FB presentation. Importantly, this effect was significant at frontal sites only, confirming a clear regional specificity. Moreover, this state-response metric of cortical activity was shown to be reliable and highly consistent across trials, for any site considered.

The observation of globally preserved reward-based learning at the behavioral (and FMT) level in MDD in our study is actually in line with some previous results reported in the literature showing normal learning performance during standard RL tasks with this emotional disorder (Cavanagh et al., 2011; Kunisato et al., 2012). To explain this result, three methodological elements are worth considering in the present case. First, we used a probabilistic learning task (Eppinger et al., 2008; Frank et al., 2005) based on “explicit” RL. Instructions clearly emphasized that the task was precisely about discovering different hidden S-R associations across successive trials, and that reward delivery directly depended on the ability to do so. By comparison, other studies (Pizzagalli et al., 2008; Whitton et al., 2016) that reported impaired RL in MDD at the behavioral and neural levels usually used “implicit” task and reinforcement. In these cases, reward was used to promote an implicit response bias (i.e., conditioning), while its delivery was actually decoupled from the task instructions. As a result, different learning mechanisms are probably involved in these two situations (Berridge & Robinson, 2003), and MDD might influence one of them only or more strongly than the other (i.e., when an implicit learning task is used primarily to promote reward-based learning). Second, behavioral impairments during RL found in MDD might actually depend not only on the type of RL task used, but also the nature of the reinforcer used to foster learning. We used so-called “primary” reinforcers (correct

vs. incorrect response, hence related to self-efficacy) whereas behavioral impairments seen in MDD patients during RL in previous studies (see above) were usually observed when "secondary" reinforcers, such as small monetary reward, were used. Third, we cannot rule out the possibility that this discrepancy between the present and some previous studies might be explained by the patients' characteristics to some extent. Although our sample of MDD patients was relatively large and homogenous (see Table 1), yet these patients were treatment resistant, severely anhedonic, and hence not immediately comparable to MDD patients tested in earlier studies where different inclusion criteria were used (Cavanagh et al., 2011; Pizzagalli et al., 2008; Treadway et al., 2012). In this context, it is conceivable that their treatment resistance, combined with the fact that they were enrolled in a treatment study, may have artificially boosted specific motivation processes (such as their engagement in the task and willingness to perform well), eventually explaining why we failed to reveal clear deficits at the behavioral level during RL in these patients using this specific probabilistic learning task.

Our results suggest that impaired RL might not be a core feature of unipolar major depression and anhedonia. Accordingly, they align with recent neuroscientific evidence indicating that this mood disorder does not impair the main expression of dopaminergic-related RPE signals (Rutledge et al., 2017), which underpin RL. In comparison, the abnormal frontal Alpha asymmetry found in these MDD patients could reflect motivational deficits, in agreement with many earlier studies and models available in the extant literature (Allen, Urry, Hitt, & Coan, 2004; Coan & Allen, 2004; Davidson, 1998b, 2004; E Harmon-Jones & Allen, 1997). Together, our new findings suggest the existence of two dissociable brain systems supporting RL: a cognitively driven approach-motivation system which is probably impaired in MDD, and a corticostriatal dopaminergic reward network, which can be globally spared in this specific mood disorder. However, additional empirical work is needed to corroborate this

conclusion, preferably using imaging methods such as fMRI (in combination with EEG), which is appropriate to determine the respective contribution at the anatomical level of these two non-overlapping brain networks to RL, as well as their differential vulnerability to MDD.

Although the current results await replication in new samples of MDD patients, they also have indirect clinical implications. In light of this dissociation outlined above, we surmise that therapies targeting a restoration of frontal lobe functioning in treatment resistant MDD patients, such as TMS (Fox, Buckner, White, Greicius, & Pascual-Leone, 2012) or the combination of neurostimulation with cognitive control training for example (De Raedt, Vanderhasselt, & Baeken, 2015), as well as interventions that may alter indirectly EEG asymmetry by improving motivation such as cognitive behavior therapy (Moscovitch et al., 2011), might all help to improve approach motivation in the first place, and subsequently counteract a drop in the sustained exploration of low reward cues in the environment. Accordingly, it would be valuable in future studies to compare RL using the same electrophysiological components as used here (i.e., FMT and frontal alpha asymmetry) before and after treatment or psychotherapy.

Last, at the methodological level, our study also adds to the existing EEG literature on RL by showing the added value of a careful exploration and modelling of FMT power changes across successive trials. Clear and compelling group differences emerged in the random condition when we examined the evolution of FMT power across time, unlike standard averages where they were less visible. These differences suggested indirectly that MDD patients failed to maintain a high level of cognitive control throughout the experiment when RL was challenging, which is consistent with a motivational impairment in these patients. We believe that this methodological approach is valuable because a careful analysis of the evolution of FMT power changes across successive trials can reveal the temporal dynamic of RL, and its modulation by MDD. Moreover, the

use of a Bayesian multilevel modelling allows to deal with these (noisy) single-trial data, as well as to quantify the evidence for a given hypothesis in terms of probability.

5.1. Conclusions.

The results of this study suggest that RL can be globally spared in MDD at the behavioral level. At the electrophysiological level, we found that FMT power substantially changed as a function of reward probability (thereby paralleling the behavioral results), and in accordance with the evidence available: while it augmented with increasing reward probability at the response level (internal monitoring), the reverse effect was found at the feedback level (exploration), suggesting a flexible engagement of this neurophysiological signal to optimize learning. These neurophysiological effects were similar for MDD patients and HCs in our study. However, when we examined FMT power changes at the single trial level when RL was challenging (i.e., reward probability was at chance level), MDD patients showed a steeper decrease across time than HCs, suggesting indirectly a drop in the ability to maintain a high level of cognitive control throughout the experiment in this condition, and hence the presence of a specific motivational deficit in these patients. Moreover, when focusing on frontal Alpha power, computed as a global state measure, or response capability throughout the experimental session, clear group differences emerged as well. More specifically, MDD was associated with a larger inhibition of the left prefrontal cortex that yielded a pronounced frontal Alpha asymmetry compared to HCs, confirming a general deficit in approach motivation in these patients (Coan & Allen, 2004; Davidson, 1998b). The present study helps to clarify the neurophysiological mechanisms of RL and approach motivation, and suggests that MDD can alter the latter while leaving the former globally spared.

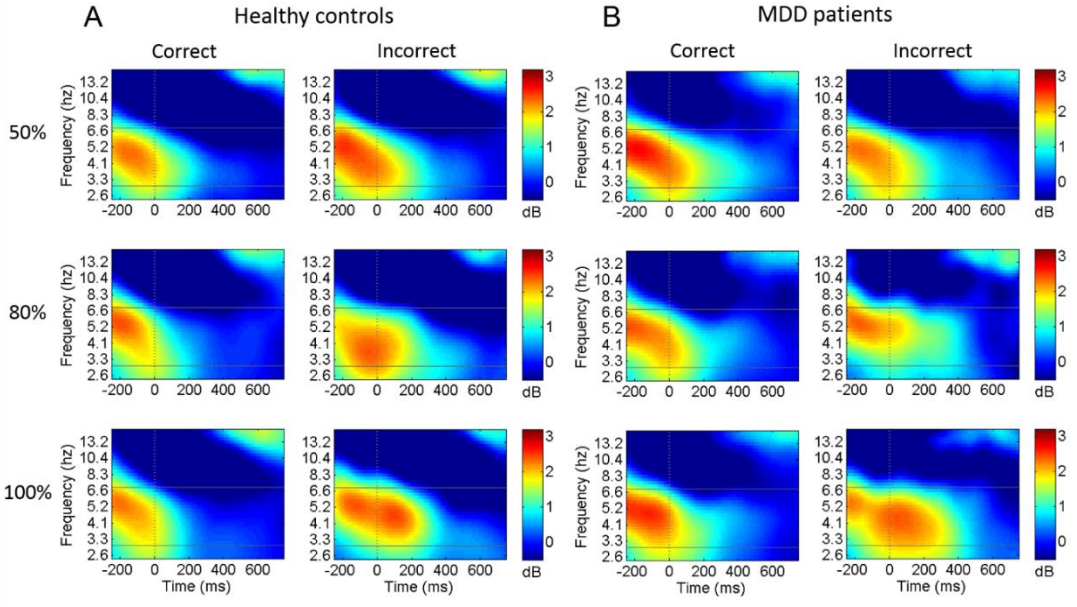
6. Supplementary Material

Supplementary Table 1.

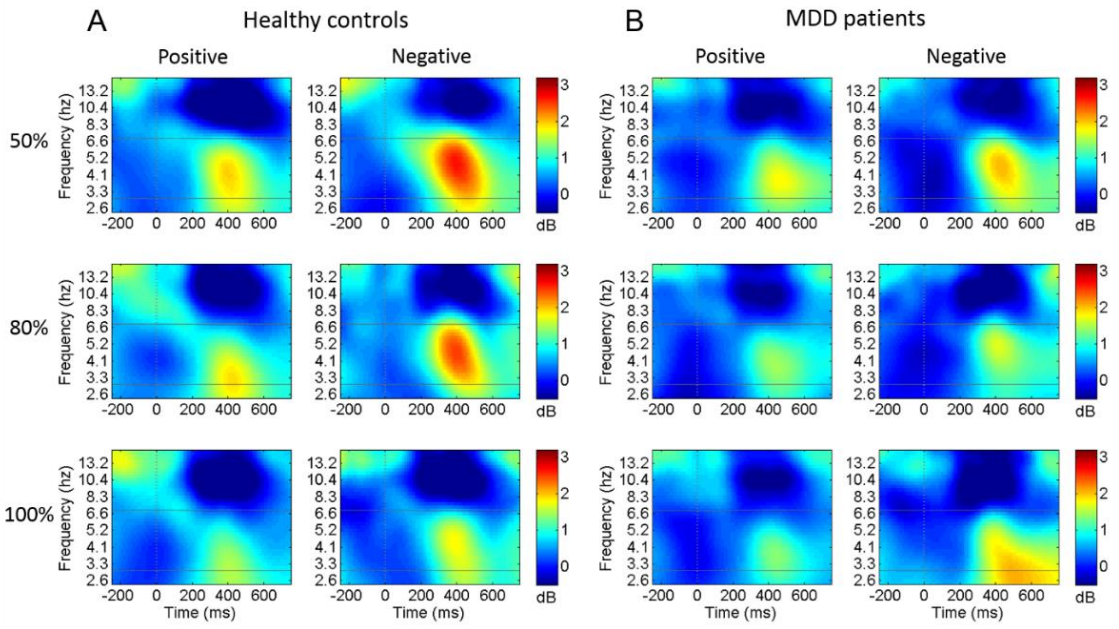
trial count

HC	resp						FB					
	correct			incorrect			positive			negative		
	100	80	50	100	80	50	100	80	50	100	80	50
average	63,1	61,6	61,7	31,4	32,3	62,9	63,0	61,4	61,6	31,2	32,5	62,9
std	3,6	5,6	4,0	12,4	15,6	3,8	3,6	5,9	4,0	12,5	15,9	3,7
max	70	70	68	57	64	70	70	70	68	57	64	70
min	56	44	53	6	9	54	56	44	54	6	9	55

MDD	resp						FB					
	correct			incorrect			positive			negative		
	100	80	50	100	80	50	100	80	50	100	80	50
average	58,6	58,4	57,5	31,9	26,3	58,2	59,5	59,3	58,3	32,2	26,7	59,0
std	6,4	6,4	7,0	14,8	11,6	6,4	6,8	7,0	7,9	14,5	11,2	6,8
max	68	68	68	62	53	68	71	71	71	62	47	71
min	42	42	39	5	8	42	41	41	37	6	8	41



Supplementary Fig. 1 (a) FMT (3 to 7 Hz) power at electrodes Fz and FCz (combined) for HCs (n=34), separately for correct and incorrect response, and for each reward probability. (b) Same analysis for MDD patients (n=34). Note that FMT power increased already before response onset, for both correct and incorrect responses. In this pre-response time-window (-300 – 0ms) no clear difference between correct and incorrect responses was found. FMT was extracted in the post-response time window (0 – 200ms), where it increased with increasing reward probability after incorrect responses selectively, and similarly between both groups.



Supplementary Fig. 2 (a) FMT (3 to 7 Hz) power at electrodes Fz and FCz (combined) for HCs (n=34), separately for positive (correct) and negative (incorrect) FB, and for each reward probability. (b) Same analysis for MDD patients (n=34). Note that MDD patients showed FMT power increases after both positive and negative feedback. However, unlike HCs, they did not clearly discriminate between them, especially when reward probability was low (i.e. probabilistic and random conditions).

6.1. Single-trial FMT power analysis.

This analysis aimed to evaluate the evidence in favor or against the hypotheses that MDD patients showed a steeper decrease in FMT power across successive trials compared to HCs when RL was difficult (random condition), and that this difference was larger for incorrect than correct FB. The random condition (50% reward probability) was optimal for this single trial analysis since it provided a high and similar amount of trials for both correct and incorrect FB (see supplementary Table 1). First, from the clean epochs (50% condition from the FB-locked dataset), we sorted out correct and incorrect FB, separately for the first and second task block (where a new set of stimuli was presented). We ordered them according to their actual position in the trial series relative to the first trial of each block, and exported the latency information of each FB. The corresponding ERP activity (i.e. from correct / incorrect FB, first / second block) was subtracted from each single epoch. Then, the same time-frequency decomposition as described in the main text was performed, but this time single-trial measures were stored (this was done for channels FCz and Fz only). Finally, power was computed as the squared modulus of the complex signal obtained, a trial-wise baseline normalization was applied (-1700 to -1500 ms pre-FB), and the resulting power ratio was log transformed (dB conversion). The power values obtained for FCz and Fz were pooled together, and then averaged in the pre-defined time/frequency window (see Material And Methods section). Last, for each accuracy level (correct and incorrect FB) and task block (1st and 2nd), the data was combined with the FB latency information, so that each single-trial FMT power measure was associated with the amount of time (rounded to seconds) elapsed from the beginning of each task block.

6.2. Statistical analyses.

Single-trial FMT power was analyzed using linear Bayesian Multilevel Models (BMLM), implemented in R (R Core Team, 2017) with the "brms" package (Bürkner, 2017), that interfaces R with the probabilistic programming language Stan (Carpenter et al., 2017). The analysis pipeline followed recent guidelines for implementing BMLM analyses with brms (Nalborczyk, Batailler, Loevenbruck, Vilain, & Bürkner, n.d.; Vasishth, Nicenboim, Beckman, & Li, 2018), and involved: i) defining a probability model; ii) computing the posterior distributions for each parameter defined by the model (i.e. the updated knowledge/uncertainty about a parameter, given the data and the prior information); iii) evaluating the fit and the predictive performance of the model. Different, theoretically sound models were compared, and iv) hypotheses were tested relying on the posterior probability distributions derived from the elected (best) model. For details, see the R code at https://osf.io/9vsdy/.

6.2.1. Model definition.

Six models of increasing complexity were fitted to the data to predict the single-trial FMT power evolution across time. Taking advantage of the flexibility inherent in multilevel modelling (i.e. estimating effects of processes that occur at different hierarchical levels), the models tested included both constant and varying effects. In the context of this analysis, the constant effects were those shared across participants (e.g. dependency on group or condition), and are also called population-level effects. The varying effects were instead specified at the individual level, allowing to model each subject variability. Given the scope of this analysis, all models (except the first) included the constant effect Time. In addition, increasingly complex models included constant effects of Accuracy and/or Group, and one or more interactive effects between them. To note, Time

was specified as a (continuous) numeric predictor, while Accuracy and Group were categorical predictors.

The first was a simple intercept model. It was devised as a benchmark model to be compared with more complex ones. The second model included the constant effect of Time; this model accounted for any global effect of Time, as well as for random variation in this effect across subjects. The third model included constant effects of Time and Accuracy, and their interaction. The fourth model included constant effects of Time and Group, and their interaction. The fifth model included constant effects of Time, Accuracy, Group, the interaction between Time and Accuracy, and the interaction between Time and Group. The sixth model included additionally the constant three way interaction of Time, Accuracy and Group.

As reported in Supplementary Table 2, all the models fitted included a constant and varying intercepts, accounting for individual differences in overall FMT power changes. Also, all models included varying slopes for all the respective within-subject constant effects (e.g. main effect of Time, Accuracy, or interactive effect of Time and Accuracy), modeling their variability over subjects. The concurrent modelling of effects couched in different hierarchical levels allowed a better estimation of the global (constant) effects of interest, thanks to the mutual sharing of variance information between the levels (partial pooling strategy; Nalborczyk et al., n.d.). For instance, this approach can minimize the impact of outliers on the estimation of the constant effects (McElreath, 2016).

6.2.2. Model fitting.

Four Markov Chain Monte Carlo (MCMC) algorithm simulations (chains) were run for approximating the posterior distribution for each model. Each chain included 2000 iterations in a multi-dimensional space

(of which, 1000 for warmup), and the frequency distributions from the resulting 4000 post-warmup samples were assumed as posterior plausibilities of the parameters specified in each model (McElreath, 2016). For all the models we used default priors in brms (i.e. weakly informative) and a Normal (Gaussian) response distribution. The convergence of the simulations (i.e. whether their estimated samples got “stably close” to the target distribution) was evaluated by examining the Rhat index (potential scale reduction factor; Gelman & Rubin, 1992), the trace plots of the chains (Bürkner, 2017), and the effective sample size of the posterior distribution of each parameter (Vasishth et al., 2018).

6.2.3. Model comparison.

The accuracy of the models in simulating the generative process under scrutiny was measured by considering their out-of-sample predictive performance (McElreath, 2016), as approximated with a leave-one-out cross-validation procedure (LOO-CV, Vehtari, Gelman, & Gabry, 2017) implemented in brms. This index provides an estimate of how well the model predicts data that have not been observed. We also evaluated the models’ fit to the observed data using the Bayesian R2 (Gelman, Goodrich, Gabry, & Ali, 2017). The joint examination of these two indexes provides a simple way to assess overfitting (over-specification of parameters; e.g. the model performs well in explaining observed data, but is worse than simpler models in predicting new data). The most accurate model was selected based on the lowest LOO-CV. In case two or more models showed comparable predictive performance, the model with best fit to observed data (Bayesian R2) was considered for the following hypothesis testing.

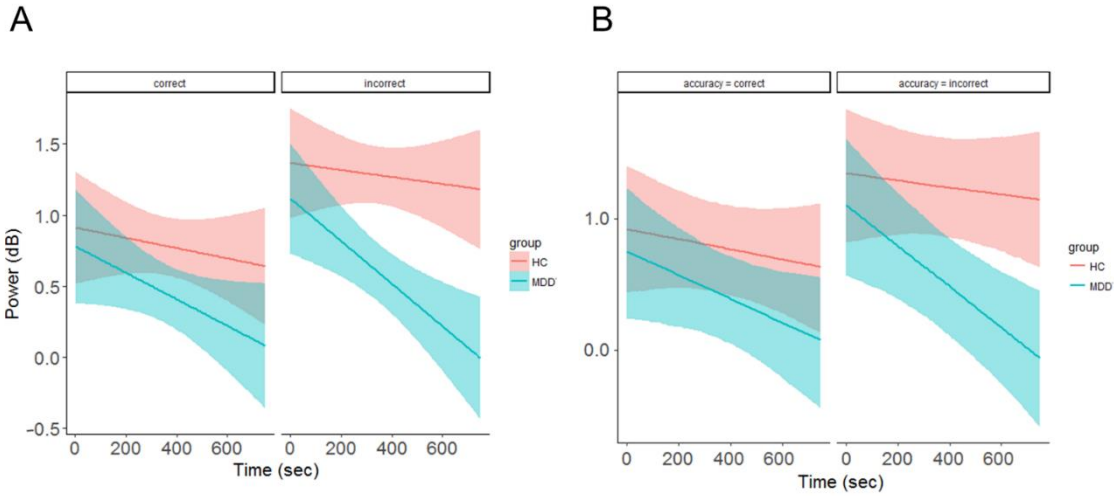
6.2.4. Hypothesis testing.

The current analysis focused on the comparison between conditions of interest with regard to the effects of the numeric predictor Time (i.e. the estimated decrease of FMT across time, rather than the estimated FMT power at a given time point). First, we built the posterior distribution of each condition of interest (i.e. the population-level marginal effects) by summing the estimated posterior samples for the constant effect Time and/or the interactions between Time, Group and Accuracy. Second, for each contrast of interest, we computed the difference between the posterior probability distributions of the relevant conditions (e.g. condition A – condition B). Each hypothesis was tested relying on the distribution of the resulting posterior samples with respect to zero. In particular, we calculated evidence ratios by dividing the amount of posterior samples below and above zero, and we formulated probabilistic statements about the evidence in favor of one hypothesis (minuend condition A being larger than the subtrahend B) relative to the alternative one (subtrahend B larger than minuend A).

6.3. Results.

Suppl. Table 2 shows the results of these models' comparisons. All the more complex models showed a better predictive performance compared to the first model. Numerically, the third, the fifth and the sixth models showed the smallest LOO-CV, but any conclusion about their effective increased predictive performance was hindered by the uncertainty (standard error; SE) of the LOO-CV estimate. As can be appreciated by the ΔLOO-CV, the difference between the sixth and any other simpler model (except for the first) was smaller than the standard error of the difference (ΔSE). Similarly, the sixth model showed the highest fit to observed data (Bayesian R2), yet not clearly different from the fifth or

third models, when considering the SE. It should be noted, however, that the most complex model (sixth) did not perform worse than the simpler ones (i.e. it did not overfit the data), despite the fact that predictive performance estimated by the LOO-CV penalizes model complexity. Given that the scope of this analysis was to evaluate alternative hypotheses about FMT power decrease over Time as a function of Group and/or Accuracy (i.e. explanation, rather than prediction per se), we used the sixth model for further hypothesis testing. Suppl. Fig. 3 shows the comparison between the observed data (fitted with simple linear models) and the population-level (constant) marginal effects from the posterior distribution estimated by the sixth model.



Supplementary Fig. 3 (a) Observed data. Linear regressions are fitted for each group / condition. The shading represents the 95% confidence intervals. (b) FMT power predicted by model 6. Population-level marginal effects of the predictors time, accuracy and group on the estimated FMT power. The shading represents the 95% credible intervals.

Supplementary Table 2

Model comparison

Model n.	Model definition in *brms*
1	power ~ 1 + (1 | snG)
2	power ~ 1 + time + (1 + time | snG)
3	power ~ 1 + time*accuracy + (1 + time*accuracy | snG)
4	power ~ 1 + time*group + (1 + time | snG)
5	power ~ 1 + time*accuracy + group + time:group + (1 + time*accuracy | snG)
6	power ~ 1 + time*accuracy*group + (1 + time*accuracy | snG)

Model n.	LOO-CV	SE	ΔLOO-CV	ΔSE	Bayesian R^2	SE
1	53203.32	133.39	-18.18	11.87	0.0287	0.0037
2	53194.53	133.24	-9.39	9.65	0.0307	0.0038
3	53186.45	132.95	-1.31	4.94	0.0348	0.0042
4	53191.30	133.22	-6.16	8.53	0.0315	0.0039
5	53183.77	132.98	1.37	2.82	0.0358	0.0042
6	53185.14	132.97	0.00	0.00	0.0359	0.0042

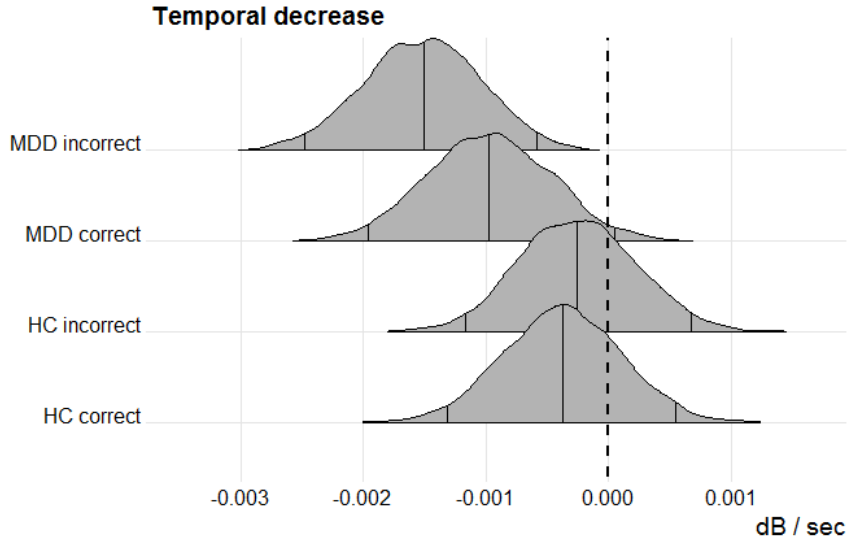
The estimations obtained from the constant effects of the sixth model are summarized in Suppl. Table 3, which includes the mean and the lower and upper bounds of the 95% credible interval (CrI) of the posterior distributions (95% highest posterior density), for each group and condition; specifically, the table reports the estimated decrease of FMT power across time (see also Suppl. Fig. 4). For illustrative purposes, Table 4 summarizes also the estimated FMT power at time “0” (see also Suppl. Fig. 5).

The analysis of the posterior distributions of this model revealed a clear effect of group on the temporal decrease of FMT power. For correct FB, the posterior distribution of the difference between the two groups [M = -0.00060; 95% CrI (-0.00195, 0.00072)] indicated that the hypothesis of a steeper decrease of FMT power across time for MDD patients than HCs was 4,05 times more likely than the alternative one, predicting an opposite effect. For incorrect FB, the same contrast [M = -0.00127; 95% CrI (-0.00266, 0.00001)] indicated that it was 34,71 times more likely that FMT power decreased across trials more sharply for MDD patients than HCs, as compared to the opposite hypothesis. These posterior distributions revealed also that Time and Group interacted with Accuracy: the difference between the posterior distributions obtained above [M = -0.00067; 95% CrI (-0.00252, 0.00115)] showed that a larger group difference in the steepness of the slope for negative compared to positive FB was 3.22 times more likely than the opposite hypothesis.

Supplementary Table 3

Estimated decrease of FMT power across time. Posterior means and 95% credible intervals for each group / condition.

Group	Accuracy	Decrease (dB/sec)	Upper bound	Lower bound
HC	Correct	-0.00038	-0.00128	0.00057
HC	Incorrect	-0.00025	-0.00117	0.00067
MDD	Correct	-0.00097	-0.00198	-0.00001
MDD	Incorrect	-0.00152	-0.00243	-0.00056

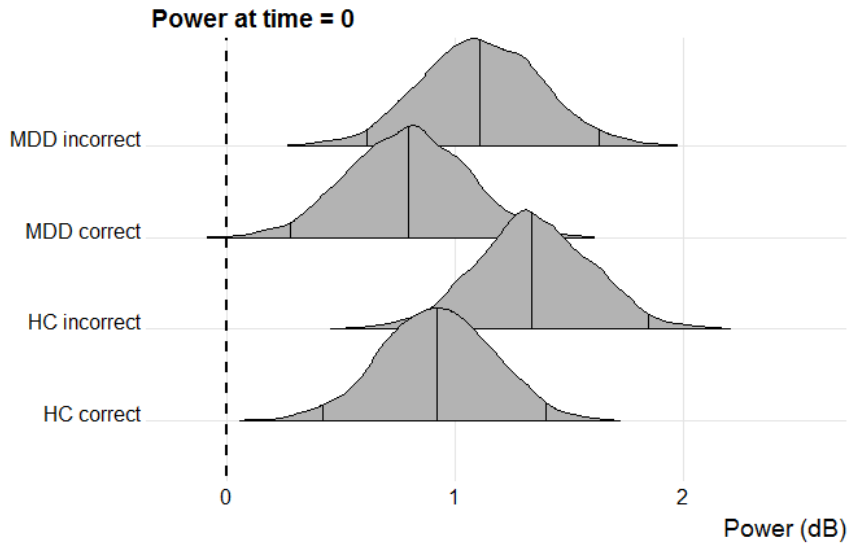


Supplementary Fig. 4 Posterior distributions estimating the temporal decrease of FMT power for each group / condition. The solid vertical lines represent the median of the posterior samples and equal-tailed 95% credible intervals. The dashed line shows the intercept at zero.

Supplementary Table 4

Estimated FMT power at time = 0. Posterior means and 95% credible intervals for each group / condition.

Group	Accuracy	Power (dB)	Upper bound	Lower bound
HC	Correct	0.921	0.418	1.390
HC	Incorrect	1.350	0.851	1.860
MDD	Correct	0.790	0.300	1.300
MDD	Incorrect	1.120	0.615	1.630



Supplementary. Fig. 5 Posterior distributions estimating FMT power at time = 0 for each group / condition. The vertical lines represent the median of the posterior samples and equal-tailed 95% credible intervals. The dashed line shows the intercept at zero.

6.4. R packages.

Brms (Bürkner, 2017)

Ggplot2 (Wickham, 2010)

Tidyverse (Wickham, 2017)

Ggridges (Wilke, 2018)

BEST (Meredith & Kruschke, 2018)

6.5. References.

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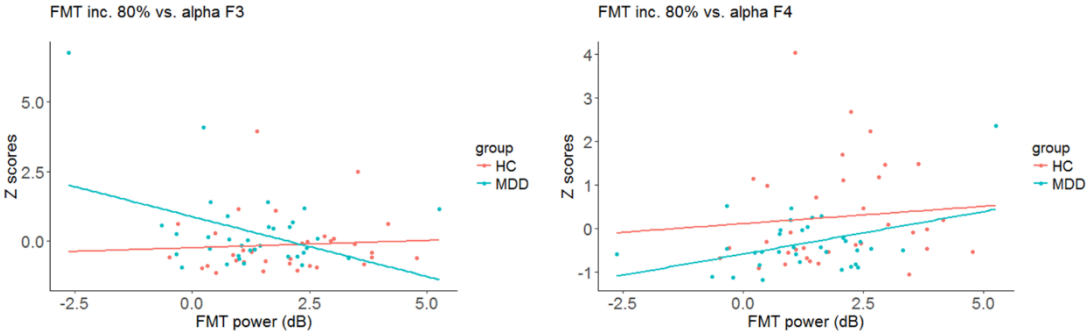
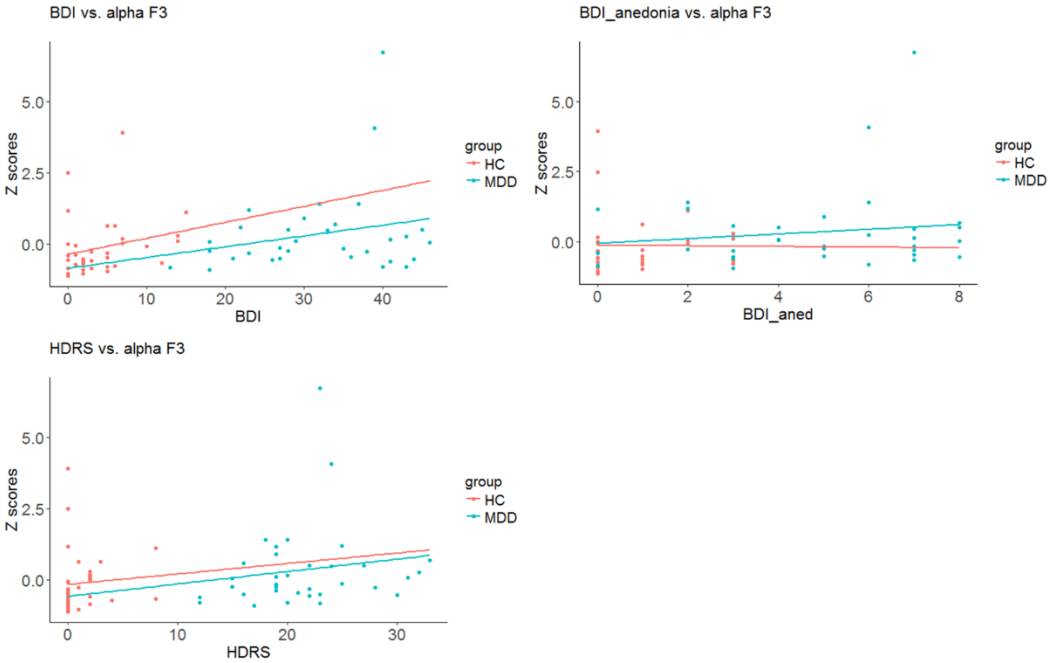
6.6. Associations between FMT, Alpha asymmetry and clinical scales

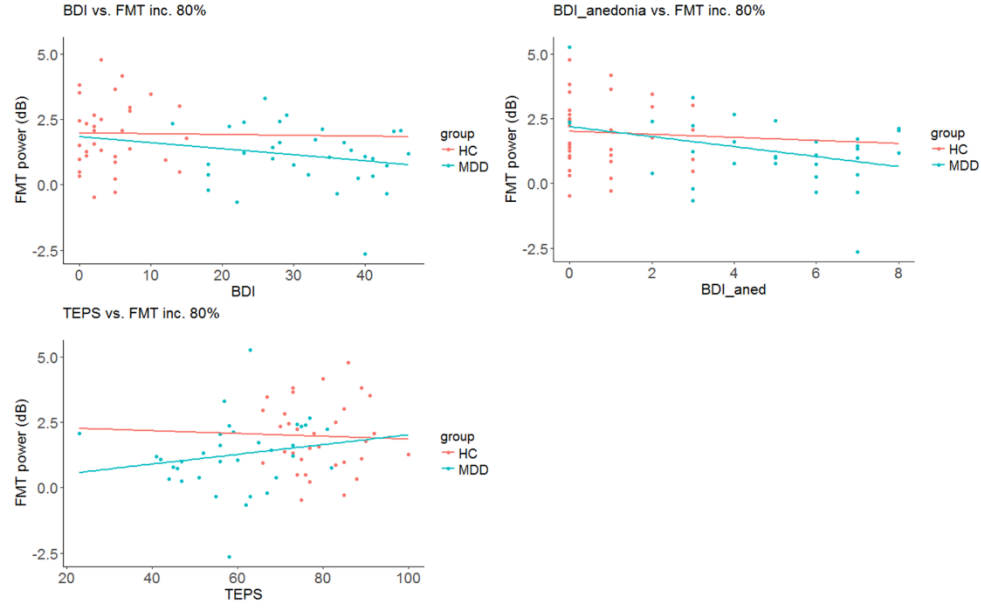
Correlation analyses were run to explore possible associations, across the whole sample (N = 68), between FMT after negative FB and normalized Alpha power at F3 and F4. An opposite association emerged between FMT (in the probabilistic condition) and normalized Alpha at F3 (negative correlation: r = -0.240, p = .048) or F4 (positive correlation: r = 0.259, p = .033), suggesting a link between FMT power changes and lateralized prefrontal cortex activation across the task (Suppl. Fig. 6). Finally we explored if symptomatology or severity of depression (based on the clinical scales used: BDI, HDRS, TEPS, SHAPS and their subscales) correlated with these electrophysiological measures (Suppl. Fig. 7 and 8). Given the skewed distribution of the clinical scales across the whole sample, non-parametric correlations by means of Spearman's Rho were used. The BDI scale was positively correlated with left frontal normalized Alpha power (F3: rs = 0.349, p = .004), and negatively correlated with FMT after negative FB (in the probabilistic condition: rs = -0.287, p = .020). The same associations were found for the BDI items related to anhedonia (F3: rs = 0.275, p = .023; FMT probabilistic condition: rs = -0.323, p = .007). Similarly, the HDRS scores were positively correlated with left frontal normalized Alpha power (F3: rs = 0.348, p = .004). FMT after incorrect FB in the probabilistic condition was also positively correlated with the TEPS scale (rs = 0.260, p = .032), and the anticipatory anhedonia subscale (rs = 0.262, p = .031).



Supplementary. Fig. 6 Associations between FMT for incorrect FB in the probabilistic condition (80%) and normalized Alpha power at F3 and F4. The direct relationship between frontal left hemisphere activation and induced FMT elicited by the FB presentation (in the probabilistic condition) aligns with the putative functional connectivity between medial frontal (e.g. ACC) and lateral prefrontal areas (DLPFC) within the action-monitoring network. Specifically, some theoretical views propose that the amount of engagement in demanding cognitive task may be regulated by the ACC by computing its current value (Cavanagh, 2014; Holroyd & Umemoto, 2016), while FMT is thought to constitute the biophysical mechanism deputed to the propagation of such FB-related information, as previously demonstrated with intracranial recordings (E. H. Smith et al., 2015).



Supplementary. Fig. 7 Associations between clinical scales and normalized Alpha power at F3.



Supplementary. Fig. 8 Associations between clinical scales and FMT power for incorrect FB in the probabilistic condition (80%).

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Chapter 6: General discussion

1. General Summary

Human behavior is driven by the pursuit of rewards. In daily life, however, reaching desired goals mostly come at a cost, often requiring effort's exertion. Accordingly, the trade-off between expected cost and benefit constitutes a fundamental aspect of motivation. This doctoral thesis focused on the neurocognitive basis of reward processing and motivation in humans. Hedonic and motivational processes, i.e. our ability of experiencing pleasure and investing energy in rewarding activities, are underestimated variables for well-being and productivity in our daily life. As a matter of fact, impairments in these specific domains (hedonic and motivation) are core aspects of psychopathology that cut across diagnostic categories (Barch, Pagliaccio, & Luking, 2016), and are particularly prominent in major depressive disorders (MDD) (Pizzagalli, 2014).

In this work, we addressed these issues from a specific angle, namely using electrophysiology. More precisely, the electrophysiology of performance monitoring (PM) offers a window onto the time-resolved neurophysiological mechanisms of reward processing, cognitive control (CC), and motivation. First, we gained insight into the functional significance of standard electrophysiological signatures of PM, when feedback (FB) provides the key stimulus that guides this process. Second, we leveraged on these markers to unveil neural mechanisms of reward and effort integration, and eventually harnessed them in psychopathology, to demonstrate the nature and extent of motivational impairments in MDD during reinforcement learning (RL). These markers of PM include, among others, the Reward Positivity (RewP) event-related component of the human electroencephalogram (EEG), closely associated to reward sensitivity (Proudfit, 2015), as well as oscillatory signals such as Frontal Midline Theta (FMT); this latter tapping into the cognitive counterpart of PM (i.e. it reflects the need for increased CC; Cavanagh & Frank, 2014). After investigating the functional significance of the FRN/RewP ERP

component against the main theoretical accounts (chapter 2), we used it to explore the integration of reward with effort information. As briefly outlined above and in the general introduction (chapter 1), such integration is crucial for cost/benefit computations, on which motivational processes heavily rely. Besides targeting this specific ERP marker of reward processing at the FB level during a previously validated gambling task, we also analyzed concurrent changes occurring in the entire EEG spectrum and that cannot be captured by a standard ERP analysis on which the FRN/RewP is based (chapters 3 and 4). This approach allowed to identify specific modulation in FMT power as a function of FB outcome and expectancy, that we confirmed was compatible with a surprise signal reflecting the need for CC when the outcome (FB) deviated from expectancy. Accordingly, we eventually adopted FMT power to demonstrate motivational impairments during RL in MDD (chapter 5).

2. Summary Of Main Findings

In chapter 2, we set out a methodological study aimed to clarify the functional significance of the FRN/RewP ERP component elicited during PM at the FB level. We manipulated the valence (i.e. monetary win vs. no-win) and the expectancy (i.e. actual reward probability) of the FB in a gambling task, and analyzed FB-locked EEG activity comparing two traditional scoring methods, both based on single electrodes, with a topographic ERP mapping analysis that takes into account the entire electric field and hence all channels available, 64 in our case. This way, we sought to gain insight into the actual sensitivity of this specific ERP component to the interactive effect of valence and expectancy; a question that has long been debated in the existing psychophysiology literature. Moreover, the use of an advanced topographic ERP mapping analysis allowed us to investigate the respective influences of valence and expectancy, as well as their likely interactions, on the temporal evolution of the entire electric field across the scalp, starting from FB onset and up to one second following it. Hence, we could test whether positive or negative (i.e. no-reward) outcome generated a single ERP component, characterized by comparable latency, scalp distribution, polarity, and differing solely in amplitude, or instead two distinct components with dissociable topographies, thereby implying non-overlapping neural generators. First, the conventional ERP analysis showed that the sensitivity of the FRN/RewP component to the interactive effect of FB outcome and expectancy actually depended on the scoring method adopted (i.e. peak to peak vs. mean amplitude), which might explain some of the inconsistencies reported for this specific interaction effect in the extant literature. Second, the topographic ERP mapping analysis identified two dominant topographies during the time-interval corresponding to the FRN/RewP component. These distinct topographical maps showed opposite valence effect, and a different sensitivity to expectancy, leaning in favor of the hypothesis of different neural generators implied in

processing positive and negative FB. For no-reward FB, the dominant topography showed a short-lasting fronto-central negativity, generated around 220 ms after no-reward FB onset, and weakly modulated by FB expectancy. Conversely, the main topography associated with reward FB was highly sensitive to FB expectancy, and crucially showed a central positivity that encompassed a longer time-frame than the concurrent one (no-reward FB), including the conventional latencies of both FRN/RewP and subsequent P300-like component. Source estimation of the ERP activity in this time-frame suggested the ACC as main intracranial generator for no-reward, while the posterior cingulate cortex was likely involved in reward FB. More generally, the results of the topographic ERP mapping analysis suggested a two-stage process during evaluative FB processing (Fouragnan, Retzler, Mullinger, & Philiastides, 2015; Fouragnan, Retzler, & Philiastides, 2018), whereby an early categorization of the outcome (i.e., valence) is followed later by the processing of its deviation from expectations (i.e., salience, or unsigned prediction error - PE). Because these results suggested the existence of two dissociable neural sources or networks implied in processing positive and negative FB during PM, they leaned against the assumption that the FRN (referring here to the negative deflection – N200-like component – generated by negative FB 250-300ms after FB onset over fronto-central electrodes) and RewP (positive deflection generated by positive FB at the same location and during the same interval) are both the neurophysiological expression of a unique or shared ERP component, which solely varies in amplitude as a function of FB outcome and FB expectancy. Relatedly, they also spoke against the use of a difference wave approach when scoring these two ERP component(s), which was an important methodological implication of these results. We incorporated this warrant when scoring and interpreting these component(s) in the subsequent chapters. Nevertheless, there, we did not simply dismiss the single ERP component hypothesis, also given some caveats associated with the use of the

topographic ERP mapping analysis (see below for further discussion). For the sake of consistency with the literature, from here on we use the term FRN to refer to both deflections elicited by positive or negative FB, when scored it with a peak-to-peak approach. For the same reason, we refer to RewP as the same component scored with a mean-amplitude approach.

In chapter 3, we manipulated again FB valence and expectancy using a similar gambling task. Additionally, we adapted the original task (Chapter 2) and introduced a cost manipulation. In specific trials, we cued participants about the possibility of playing the gamble a second time in case of no-reward FB after the first attempt. However and crucially, if willing to do so, participants were first required to expend effort in an additional task (i.e. an orthogonal dot-clicking task), before being allowed to resume the gambling task and give it a second try. With this design we could explore the influence of effort anticipation on need for control (FMT power) and reward processing (e.g., RewP). First, we corroborated the hypothesis that the FRN modulation behaves according to a signed PE, and is thus compatible with the RPE framework (Holroyd & Coles, 2002). FMT power did show sensitivity to FB outcome and expectancy but, at difference with the FRN, did not show an interactive effect between these two factors, hence it was compatible with an unsigned PE (i.e., salience, or surprise signal). Second, we failed to evidence any reliable effect of effort anticipation on control signals (FMT power), when the FB turned out to be no-reward and hence cued participants about ensuing effort. Rather, effort anticipation influenced reward processing selectively, by increasing reward valuation of the FB (at the RewP level) when effort was anticipated, but eventually avoided. This effect was evidenced by comparing reward FB when effort anticipation was induced or not. In both cases the same monetary win was actually obtained, and both trial types ended without further effort requirement. Crucially, in the former type of trial, the reward FB additionally signaled that the anticipated effort expenditure was precluded. Accordingly, effort avoidance seemed to bring about increased

reward processing, as reflected in the modulation of EEG markers previously associated with reward processing, including the RewP component, but also power increases in Delta and Beta-gamma frequency bands which are complementing neurophysiological signals of reward processing. We corroborated the interpretation of this effect with a follow-up behavioral experiment, where participants reported at the subjective level increased hedonic value for reward after effort anticipation (and avoidance), compared to simple reward. In sum, we provided novel electrophysiological evidence that reward and effort anticipation are integrated during PM at the RewP level, and more specifically that effort information can influence the affective value of the outcome rapidly after its onset, given that this ERP component reaches its maximum amplitude ~250 ms after FB onset. More broadly, increased reward processing with effort avoidance, as observed in chapter 3, was consistent with the effort-discounting framework (Bonnelle et al., 2015), according to which reward is usually devalued by the effort required to obtain it. These results were also consistent with the assumption of an aversive nature of effort (Kool, McGuire, Rosen, & Botvinick, 2010; Kurniawan et al., 2010), and with a general principle of economy that rules decision-making (O'Doherty, Cockburn, & Pauli, 2017).

In chapter 4, we sought to conceptually replicate the main finding of Chapter 3, namely to demonstrate the integration of reward processing with effort anticipation at both the EEG and behavioral levels. Crucially, some important changes were implemented in the experimental paradigm compared to chapter 3, in order to control for potential confounds that might have influenced the results in that chapter, as well as to extend our inferences to the domain of "pure" cognitive effort, instead of opportunity cost (Kurzban, Duckworth, Kable, & Myers, 2013). In short, we investigated the effect of effort avoidance on reward processing, when comparing two effort conditions that only differed in terms of difficulty of an orthogonal effort task (implemented as arithmetic calculation this time; see

Vassena et al., 2014). At the behavioral level, participants rated the hard effort task as less pleasant than the easy one. Accordingly, when considering the more implicit influence of effort anticipation on the hedonic value of FB, evaluated by participants at a trial-by-trial level, no-reward FB was reported as more frustrating and less pleasant when high, compared to low effort, was anticipated and eventually exerted. In fact, no-reward FB implied the necessity for the participants to carry out the effort task, thereafter. This effect proved that participants did actually process cue information regarding the prospective difficulty of the effort task. In this design, the aversiveness of anticipating (and exerting) effort in no-reward FB was a condition sine-qua-non for observing a symmetrical relief effect on effort anticipation (and avoidance) for reward-FB. Nevertheless, we found only weak evidence in favor of a symmetrical modulation of reward FB, namely more positive ratings for reward FB when high compared to low effort was anticipated, but eventually avoided. Somehow consistently with this lack of clear-cut differentiation at the subjective level, when we turned to EEG markers of reward processing (e.g., RewP), we failed to evidence a reliable increase in reward processing when high compared to low effort was avoided. In chapter 4, we discussed and considered specific features of the experimental design that could have led to this outcome. We will return to this issue in section 4, taking into account the specific nature of cognitive effort as compared to other kinds of behavioral cost, such as opportunity cost. Interestingly, we found evidence of effort and reward integration during FB processing when considering the evaluative FB provided after the effort task. More precisely, larger effort expenditure increased the subsequent reward valuation (at the RewP level), in case of correct performance. These results highlighted the faceted nature of cognitive effort, whose aversiveness should not be given for granted. For instance, the hedonic value of cognitive effort anticipation may depend on contextual, as well individual determinants (Inzlicht, Shenhav, & Olivola,

2018; Westbrook, Kester, & Braver, 2013). Moreover, cognitive effort exertion may add value to the outcome of individual's actions.

In chapter 5, we leveraged on the functional role of FMT oscillations, as put forward by several theoretical models in the literature (Cavanagh & Frank, 2014; Verguts, 2017) and corroborated to some extent in the previous chapters, to investigate the neurophysiological dynamics of PM during RL. We adopted a standard probabilistic learning task, and manipulated the stimulus-response association such that three different conditions differing in terms of reward probability could be created and compared to each other at the behavioral and EEG levels. In line with previous reports (Cavanagh, Frank, Klein, & Allen, 2010; van de Vijver, Cohen, & Ridderinkhof, 2014), we found that FMT power was modulated by reward probability, with symmetrical effects between the response and the FB levels. More precisely, FMT power was maximal for incorrect responses when reward probability was high, but conversely maximal for negative FB when reward probability was low. We interpreted this pattern as the propagation back in time (from the FB to the response) of PE as a function of learning (i.e., reward probability condition). In other words, FMT power reflected the graded internalization of the corresponding stimulus-response association, in accordance with the evidence available and accumulated during RL, and consistent with behavioral data showing increased learning performance for deterministic compared to probabilistic or random stimulus-response associations. Hence, FMT power reflected learning dynamics, being consistent with the need for CC as a function of the current PE generated internally (response) or externally (FB). Moreover, FMT power exhibited a clear valence effect, being more strongly elicited by incorrect responses and negative FB, as compared to correct responses and positive FB, respectively. Notably, despite this asymmetrical sensitivity to FB valence, FMT power scaled with reward probability (i.e., expectancy) for both positive and negative FB, configuring as an unsigned PE signal (Cavanagh, Figueroa, Cohen, & Frank, 2012).

In other words, this signal may convey the need for control, as a function of the PE, regardless of the valence of the input information. After corroborating the significance of this signal in the context of RL, we assumed FMT power as a valid marker of motivation to sustain RL, and titrated RL using the same task in a sample of unipolar MDD patients, comparing them to matched healthy controls. These two populations clearly differed in anhedonic symptomatology, as further confirmed by core impairment in approach-related motivation, as suggested by asymmetric lateral prefrontal cortex (PFC) activation during FB processing (i.e., frontal alpha asymmetry; Davidson, Ekman, Saron, Senulis, & Friesen, 1990; Nusslock, Walden, & Harmon-Jones, 2015), besides standard clinical scales. During RL, somehow consistent with a spared behavioral performance, the overall pattern of FMT modulation was preserved in MDD patients. Crucially, at the FB level, MDD patients compared to controls showed a steeper decrease in FMT power across time when reward probability was low (random stimulus-response associations), especially for negative FB, suggesting a failure in maintaining enhanced CC across time in face of a challenging learning situation. In sum, we reported an overall spared RL in MDD, in the context of (explicit) probabilistic learning. At the same time, when carefully examining the temporal dynamics of RL, we evidenced motivational impairment in MDD in sustaining effortful CC and FB processing when learning was hard.

3. Reward And Expectancy: Methodological Aspects And Theoretical Implications

As one of the main objectives of the thesis was to gain new insight into the functional significance of standard and well-described EEG markers of PM, in each chapter we first sought to assess their sensitivity to both valence and expectancy of the action's outcome, as these two variables are core components of PM (Ullsperger, Danielmeier, & Jocham, 2014). We briefly discuss in this section some of the implications of the results that have emerged across the different chapters, first with a focus on the scoring and interpretation of these specific ERPs and time/frequency components, later followed by a discussion at the theoretical level of the integration of reward with effort during FB processing.

3.1. FRN/RewP.

With regard to this classic ERP elicited by evaluative FB, in Chapter 2 we highlighted the importance of computing, reporting, and systematically comparing alternative scoring methods available in the literature. In fact, we showed that the scoring method chosen could substantially influence the results, especially when it comes to evaluate the sensitivity of this ERP component to FB's expectancy. A consistent finding, across both Chapters 2 and 3 where a gambling task was used, was that the FRN/RewP robustly responded to FB valence (i.e. being more negative for no-reward than reward FB), no matter the scoring method adopted (i.e. peak-to-peak, mean-amplitude, or topographic analysis). This observation alone speaks against the salience hypothesis (Oliveira, McDonald, & Goodman, 2007; Talmi, Atkinson, & El-Deredy, 2013), according to which this ERP component would primarily reflect outcomes that deviate from expectations. Hence, the consistent modulation of this specific ERP

component with valence can hardly be reconciled with the tenets of the PRO-model (Alexander & Brown, 2011), insofar the model predicts a mPFC activity (including the ACC, corresponding to the likely source of the FRN) being functional to the detection of the violation of predictions about multiple possible action outcomes (each with a corresponding probability), but no matter their valence or direction (i.e., unsigned PE).

A less consistent finding across the different chapters was the modulation of the FRN/RewP by FB expectancy, as manipulated by changing reward probability across different conditions in the gambling task. In both chapters 2 and 3, we observed a clear interaction effect between FB valence and expectancy, but only when a peak-to-peak scoring method was used. As discussed in Chapter 2, the peak-to-peak scoring for the FRN (where the preceding P200 is used as baseline for N200 peak measurement) helps minimizing the confound of temporally overlapping ERP components, and is particularly useful when adjacent components (P200 and N200) are sensitive to the main factor of interest, namely expectancy in this case. At variance with the peak-to-peak scoring method, a mean-amplitude approach is less sensitive to high-frequency noise (Luck & Gaspelin, 2017), that may bias peak amplitude measures, especially when it varies across conditions due to different trial numbers and hence different signal to noise ratios. To address this issue, in Chapter 3 we balanced the number of trials across conditions (by randomly selecting a subset of trials from the more frequent conditions to match this number with the least frequent conditions), and still found a clear interaction effect between FB valence and expectancy. Notably, this was the case with the elected gambling task where the FB is actually not instrumental for behavioral adjustment and despite the fact that some authors questioned the validity of this task for generating expectations (Ferdinand, Mecklinger, Kray, & Gehring, 2012). Ultimately, a perfect control on subjective expectancy is virtually impossible to achieve with any experimental task, but our results did corroborate the assumption that this

component likely reflects the activity of a neural system involved in FB processing along a “better or worse than expected” dimension (Sambrook & Goslin, 2015; Walsh & Anderson, 2012). As such, the FRN/RewP component fulfils the tenets of the classic RL-ACC theory (Holroyd & Coles, 2002; Holroyd, Pakzad-Vaezi, & Krigolson, 2008), according to which the ACC responds to negative and/or positive RPE dopaminergic signals arising from the midbrain and projecting to this medial frontal cortical area where this ERP component is eventually generated. However and as mentioned above in this closing section, an important caveat is warranted in light of the results of the topographic ERP mapping analysis performed in Chapter 2. This analysis identified two distinct electric field configurations accounting for the variance in reward and no-reward FB ERP waveforms, speaking against the assumption that a unique ERP component is associated to them. A distinctive fronto-central negativity map fitted best no-reward FB data, around 277 ms after FB onset. This electric field configuration (in Chapter 2, FRN-map) failed to show a systematic modulation in explained variance with expectancy; a result at odds with the peak-to-peak ERP analyses where the valence by expectancy interaction was driven by no-reward FB. Most importantly, a central positivity map (in Chapter 2, RewP-map), that fitted best reward-FB data and was modulated by FB expectancy, surprisingly encompassed a much longer time-frame (217 – 386 ms) than the FRN-map. In sum, on the one hand the topographic ERP mapping analysis brought about results that were inconsistent with the main theoretical model available in the literature (Holroyd & Coles, 2002; Holroyd et al., 2008), since only the ERP elicited by no-reward FB seemed to be generated in the ACC. On the other hand, we contended in chapter 2 that more research is warranted before drawing such a strong conclusion, due to the limitations of this data-driven analysis. As pointed out in Chapter 2, it may be the case that the clustering algorithm underlying the topographic analysis, by taking into account the global dissimilarity of the electric field over time, may have failed in

segregating two similar scalp configurations that corresponded to different and partially overlapping ERP components elicited by reward FB: an early one, coherent with the one elicited by no-reward FB, and a subsequent one, elicited by a later parietal positivity (i.e., P300-like component). Indications of this possibility come from studies adopting the same gambling task but relying on a principal component analysis instead (Foti, Weinberg, Bernat, & Proudfit, 2015; Foti, Weinberg, Dien, & Hajcak, 2011; Proudfit, 2015), which is able to isolate a reward-related positivity in the early time-frame traditionally associated to the FRN/RewP (around 290 ms), from a subsequent positive component (P300).

3.2. FMT power.

When investigating concurrent changes in the EEG spectrum by means of time/frequency analyses, we consistently found an increase in FMT power time-locked to the evaluative FB provided in the gambling task (chapters 3 and 4), and to both response and FB in the probabilistic learning task (chapter 5). This signal included the spectral representation of the response- or FB-locked ERP activity in the theta range, as well as EEG activity non-phase locked (induced) with the onset of these events. Induced FMT power usually lasted for a few cycles, consistent with a burst of FMT oscillations commonly reported (Cavanagh et al., 2012; Cohen, Elger, & Ranganath, 2007; van de Vijver et al., 2014). FMT power was consistently larger for incorrect responses and negative FB, compared to correct responses and positive FB, respectively. Moreover, it consistently increased as inverse function of FB expectation (chapters 3 and 5), and reflected PE at both the response and FB levels during RL (chapter 5). Notably, we never found for FMT an interaction effect between response or FB valence and expectancy. In light of these observations, and of its well-described association with diverse events or contexts (Cavanagh & Frank, 2014), we argued that this signal is compatible with an unsigned

PE, primarily reflecting the computation of the need for augmented control over information processing upon the encounter of surprising events (here, unexpected outcomes). As introduced in chapter 1, FMT power is likely generated in the medial-frontal cortex, and may allow for large-scale neuronal interactions through interregional oscillatory synchronization (e.g., with control-related dlPFC) (Siegel, Donner, & Engel, 2012).

3.3. An integrative view on FB processing.

A final consideration pertains to the dissociation between FB-locked ERP (the FRN) and FMT power, whereby the first but not the latter exhibited an interactive effect between FB valence and expectancy. As argued by Hajihosseini and Holroyd (2013), the evoked and induced components of FMT may reflect different neurophysiological phenomena, at odds with the assumption that the ERPs associated with control processes and PM (i.e. N2, ERN, FRN) are merely a different (and partial) way for quantifying FMT activity (Cavanagh et al., 2012; Cavanagh & Frank, 2014). Across the different chapters, the FRN (at least when scored peak-to-peak) responded to both valence and expectancy, and their interaction, being the only marker fully compatible with a RPE framework (Holroyd & Coles, 2002). Instead, FMT power was primarily sensitive to FB expectancy (i.e., reward probability). In fact, in the context of the gambling task (Chapter 3), the main effect of valence exhibited by FB-locked FMT power was absent when isolating the induced component from the total power, and thus was selectively driven by the evoked component (i.e., the FRN). In turn, the induced component preserved a clear modulation by FB expectancy. These auxiliary results, when a decomposition of total FMT into induced and evoked components is performed, can be retrieved online (https://osf.io/z7ru2/). In the context of the evaluative FB provided in probabilistic learning task (chapter 5), we did

focus our analyses exclusively on the induced component of FMT, and yet evidenced a main effect of valence, on top of the modulation of FMT by reward probability. This result that apparently disconfirms the notion that FMT primarily reflects deviations from expectations, may actually be explained by an stronger heuristic value of negative compared to positive FB in the context of RL. In other words, evaluative FB may elicit an increased need for control when it disconfirms cached stimulus-response associations (negative FB), compared to when it corroborates it (positive FB) (Cavanagh et al., 2012).

In sum, the FRN ERP component and FMT oscillations may reflect correlated, but not interchangeable neurophysiological phenomena during PM. The first may reflect the ACC response to mesencephalic RPE signals, in accordance with the dominant RL-ACC theory (Holroyd & Coles, 2002); the latter may represent instead a common biophysical mechanism by which ACC, upon processing of incoming RPE, conveys the need for CC and behavioral adaptation (Cavanagh & Frank, 2014; see also Verguts, 2017). At difference with the FRN, FMT power captures unsigned PE, which is compatible with the tenets of the PRO-model of the ACC (Alexander & Brown, 2011), and a more recent Hierarchical RL model (Holroyd & Umemoto, 2016; Holroyd & Yeung, 2012).

3.4. Delta and Beta-gamma.

In chapters 3 and 4, beside scrutinizing specific changes in FMT power, we also systematically evaluated FB-locked spectral perturbations in an extended range of frequencies. Interestingly, we observed a reliable modulation of Delta power (0 – 4 Hz) as a function of FB valence, with larger values associated to reward than no-reward FB, and as a function of FB expectancy, with larger values associated with unexpected than expected outcome. In fact, the time-frequency analysis, at difference with chapters 3-5 in this thesis, has been sometimes adopted to parse FB-

locked evoked activity (i.e., the averaged ERP) associated either with the FRN (in the theta range) or with the following P300 (in the delta range). In analogy with the functional significance of the P300 component, Delta activity at centro-parietal channels has been adopted as a measure of sensitivity to monetary gain (Bernat, Nelson, & Baskin-Sommers, 2015; Webb et al., 2017). Perhaps more intriguingly, a clear valence effect was reliably observed in a frequency range amid Beta and Gamma (20 - 35 Hz) at fronto-central sites. Previous studies investigating this reward-related increase in mid-frontal beta activity suggested that it may reflect the engagement of a fronto-striatal-hippocampal network, involved in reward-related memory enhancement (Marco-Pallares et al., 2008; Mas-Herrero, Ripollés, HajiHosseini, Rodríguez-Fornells, & Marco-Pallarés, 2015).

4. Effort Information And Performance Monitoring

As reviewed in the general introduction, during PM the generic monitoring function of the medial prefrontal cortex, and ACC in particular, serves to detect the need for performance adjustment (Ullsperger, Danielmeier, et al., 2014). Accordingly, this area signals other brain regions that changes in CC and behavioral response are needed (Ridderinkhof, Ullsperger, & Nieuwenhuis, 2004). Thus, in this hub area, two main processes possibly converge: detecting the need for control (i.e., controlled vs. automatic information processing), and signaling the need for control to hierarchically higher areas, such as the dlPFC, to eventually aid achieving behavioral adjustment according to goals. With regard to the first process, namely RPE processing and need for control detection, a vast body of electrophysiological research endowed the FRN/RewP component with this role (Sambrook & Goslin, 2015; Walsh & Anderson, 2012). With regard to the second process, namely the communication of the need for CC, more recent theoretical propositions put forward FMT oscillations as a plausible neurobiological mechanism underpinning such inter-regional communication (Cavanagh & Frank, 2014; Holroyd & Umemoto, 2016; Verguts, 2017).

An open question that we sought to answer in chapters 3 and 4, is whether and how effort information is integrated during PM, and eventually reflected in these electrophysiological signals. First, in chapter 3, we showed that the RewP component, associated to reward processing, was also modulated by effort anticipation. More specifically, a monetary reward increased reward processing when it also precluded effort's exertion subsequently. This result has potentially interesting implications at both the theoretical and practical (clinical) levels. First, it suggests that the neural source of this signal may process not only mesencephalic RPE, but also explicit effort information. Alternatively, it may be argued that effort information, when systematically anticipated, may simply reduce the net

value of reward expectation. Hence, due to a general decrease of predicted value of the action's outcome, a reward FB implying effort avoidance could be appraised as (much) better than expected, compared to a reward FB when effort is not cued. This interpretation allows to integrate our new results with the general RPE framework (Schultz, Dayan, & Montague, 1997). Second, the sensitivity of the RewP component to effort information should be carefully considered when adopting this marker for quantifying anhedonic symptoms (Proudfit, 2015; Weinberg, Liu, Hajcak, & Shankman, 2015; Weinberg & Shankman, 2017). As a matter of fact, individual differences in RewP amplitude may reflect avoidance of cost or effort intrinsic in carrying out the task, besides reward sensitivity. Hence, alterations of this marker in anhedoinc populations (i.e. blunted RewP component) may be driven not only by reduced reward sensitivity per se, but also by more complex and abnormal motivational mechanisms, for instance an increased propensity to devalue reward as a function of their potential cost.

With regard to FMT power, in chapters 3 and 5, we provided evidence for the compatibility of this signal with an unsigned PE implicated in expectancy violations (both in a gambling task and a RL task). The modulation of FMT power with PE that emerged from our studies is very much in line with previous reports, and with the general assumption of a "surprise" code (Cavanagh & Frank, 2014). Yet, in our studies we failed to evidence a modulation of this signal by effort anticipation. With this regard, it is important to emphasize that our attempt to integrate effort information in the context of PM is probably imperfect and preliminary, and it definitely requires additional empirical validation in the future. Probably, in both chapters 3 and 4, the disclosure of effort information at the FB level did not entail a phasic recruitment of attentional resources (or any other component of CC). More specifically, in chapter 3 we manipulated effort with a dot-clicking task that did not require immediate reaction, nor the allocation of large attentional resources, and that was eventually perceived

by the participants as a neutral and time-consuming activity at the subjective level. To address this issue, in Chapter 4 we increased the cognitive load of the effort task, introducing mental arithmetic and reducing the gap between FB and effort task initiation (e.g., removing the choice to engage with effort or not). Nevertheless, there too, we failed to evidence specific FMT power increase upon a (negative) FB signaling an ensuing cognitive effort task. Notably, despite the full contingency of the effort task with the preceding negative FB (i.e. no choice was allowed), a relatively long time (about 1 second) separated the FB and the actual initiation of the arithmetic task. Although suboptimal for the sake of eliciting reactive control (Braver, 2012), relatively long intervals between FB and effort task were required for methodological reasons, including the use of time/frequency analyses. In this context, increased FMT power could rather reflect proactive control, or attentional preparation for the arithmetic task as a function of its difficulty (see Cooper et al., 2019). However, it may be that optimal performance in the arithmetic task, characterized by paced and relatively long digits' presentation, did not require specific preparatory processes, even in the hard condition. Hence, an open question is whether or not enhancing cognitive control and attention in the hard compared to easy arithmetic task were actually functional, and eventually even implemented, to maximize behavioral performance.

Surprisingly, when we changed the effort manipulation by replacing the dot-clicking task (Chapter 3) with the arithmetic task (Chapter 4), we failed to evidence a clear-cut increase in reward processing as a function of effort avoidance, both at the subjective and electrophysiological levels. As discussed in chapter 4, a parsimonious explanation of this discrepancy may be the reduced efficacy of the manipulation of cognitive effort (arithmetic task) in eliciting aversion for its exertion (and hence, in increasing hedonic feelings for its avoidance). In other words, given that a similar sample size was used in chapters 3 and 4, it is possible that a reliable effect of effort avoidance on reward processing was detected only

in chapter 3 due to the likely stronger impact of the combination of effort and opportunity cost that accompanied the execution of the dot-clicking task. Besides this consideration, it is important to mention that cognitive effort has a labile phenomenology, and can be perceived as either aversive or valuable according to the context where it is elicited or manipulated, as well as is sensitive to individual characteristics (Inzlicht et al., 2018; Mussel, Ulrich, Allen, Osinsky, & Hewig, 2016). Related to this contention, when investigating the effect of cognitive effort on reward processing and motivation in future, it will be probably important to consider and model individual differences in need for cognition (Cacioppo, Petty, Feinstein, & Jarvis, 1996; Cacioppo, Petty, & Feng Kao, 1984), intrinsic motivation (Ryan & Deci, 2000), and epistemic motivation (Mussel et al., 2016), because these dispositions are likely to influence how effort and reward interact with each other during PM.

In summary, in chapters 3 and 4 we provided preliminary evidence for the integration of reward with effort information during PM at the electrophysiological level. This integration was mostly evidenced in the modulation of the RewP component, whose amplitude increased with effort avoidance (chapter 3), but also for reward obtained after performing a hard compared to easy mental arithmetic task, and hence after enhanced cognitive effort exertion (chapter 4). Given that the likely source of this signal is the ACC, these results corroborate the hypothesis that this medial frontal area is involved in monitoring and integrating both cues, and as such, may be endowed with a key motivational role in preparing for (Krebs, Boehler, Roberts, Song, & Woldorff, 2012; Vassena et al., 2014) or sustaining effortful behavior based on its learned value (Holroyd & Umemoto, 2016); alternatively (but not exclusively), monitoring effort-demand information by the ACC may serve for reward evaluation (e.g., effort discounting; Botvinick, Huffstetler, & McGuire, 2009), and may possibly affect effort-based decision making (Floresco & Ghods-Sharifi, 2007; Rushworth, Walton, Kennerley, & Bannerman, 2004).

5. Translation To Assessment Of Anhedonia And Motivation

In light of the evidence discussed so far, some of the electrophysiological signals associated to reward processing and PM more generally, may hold promise for investigating anhedonia and motivation impairments in specific affective disorders. First, we confirmed that the FRN/RewP ERP component reliably reflects reward processing (i.e., valence) at the FB level. As discussed earlier in this thesis, the RewP is modulated not only by individual reward sensitivity (Proudfit, 2015), but most likely also by subjective cost and perceived effort that accompanies the task-related behavior. Hence, when resorting to this index in a clinical context, particular attention should be paid in controlling for cost variables in the experimental task design, as well as when interpreting results. Accordingly, the smaller FRN/RewP showed by depressed individuals compared to controls performing standard gambling tasks (for a meta-analysis, see Moran, Schroder, Kneip, & Moser, 2017) may not reflect purely reduced reward sensitivity, but also translate the influence of effort discounting on reward evaluation.

Second, in the general introduction (chapter 1) we outlined a recent paradigm shift in the conceptualization of anhedonia, highlighting the relevance of the anticipatory ("wanting") component of reward processing in psychiatric disorders such as MDD. This wanting component relates to DA-dependent I) incentive salience attributions (Berridge, Robinson, & Aldridge, 2009), II) reward learning and its influence on decision and behavioral policies (Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006; Pizzagalli, Iosifescu, Hallett, Ratner, & Fava, 2008), and importantly III) cost-benefit decision-making (Salamone, Correa, Yang, Rotolo, & Presby, 2018). We argued that motivation, quantified as the cost that one would accept to incur to attain a benefit (Pessiglione, Vinckier, Bouret, Daunizeau, & Le Bouc, 2018), does not orient only overt behavior (i.e.,

enduring physical costs or effort) (Treadway, Buckholtz, Schwartzman, Lambert, & Zald, 2009), but also cognitive effort (Apps, Grima, Manohar, & Husain, 2015) and the quality of information processing (i.e., controlled vs. automatic – the main dimension of CC; Kool, McGuire, Rosen, & Botvinick, 2010). Accordingly, several computational models of ACC function endowed this area with a pivotal role in performing a form of cost-benefit computation for optimal CC allocation (Shenhav, Botvinick, & Cohen, 2013), or more broadly in sustaining effortful behavior previously reinforced (Holroyd & Yeung, 2012; see also Verguts, Vassena, & Silvetti, 2015). Notably, FMT has been proposed as a potential marker of ACC output reflecting control over task performance, and hence cognitive effort expenditure (Holroyd & Umemoto, 2016). While we failed in confirming this hypothesis when manipulating effort anticipation in a rather complex experimental design (chapter 4), yet there is growing and independent evidence showing a modulation of this signal by cognitive effort exertion (Mussel et al., 2016), particularly during working memory maintenance and retrieval (Hsieh & Ranganath, 2014), and in tasks that more closely tap on CC components (e.g., task shifting; Cooper et al., 2019, 2015). Moreover, as discussed above, short bursts of FMT power reflect learning processes at both the response and FB levels (van de Vijver et al., 2014), acting as a unsinged PE (Cavanagh & Frank, 2014). As such, FMT power holds considerable promises for the assessment of motivation, when conceived as the maintenance of cognitive demanding operations over time (see also Umemoto, Inzlicht, & Holroyd, 2018), in face of variable intrinsic or extrinsic rewards. Capitalizing on this rationale, in chapter 5 we measured phasic FMT power oscillations elicited by response and FB during a probabilistic learning task, and compared unipolar MDD patients with matched healthy controls. As a matter of fact, a robust group difference was evidenced not in terms of behavioral performance, nor in the learning-related pattern of FMT power, but specifically in the capability of maintaining elevated FB-locked FMT activity over time when learning

was hard because reward probability was low (i.e., the stimulus-response association was random). Accordingly, the drop of FMT power for MDD patients plausibly reflected a decaying PM, and more precisely impaired ability to recruit and maintain control over information processing, in updating stimulus-response associations, and eventually sustain effortful learning over time. These results are consistent with the hypothesis that MDD does not specifically or exclusively impair RPE signaling and reward-based learning (Bakic et al., 2017; Rutledge et al., 2017), whereas it may more strongly alter motivational processes such as incentive salience attribution to stimuli (that promotes approach behavior; Berridge et al., 2009), and/or cost/benefit decision making (about control allocation, in this case; Botvinick & Braver, 2015; Pessiglione et al., 2018).

6. Limitations

Alongside specific methodological limitations pertinent to each specific chapter, and discussed so far, a general caveat is worth to be explicitly addressed in this closing section. In chapter 1, we defined PM as the process by which an agent detects the need, type and magnitude of adaptive control and behavioral adjustment (Ullsperger, Fischer, Nigbur, & Endrass, 2014) during goal-directed behavior. In this context, we conceptualized control mainly along an automaticity dimension (i.e., controlled vs. automatic information processing), hence bridging this concept to what is often referred to as CC in terms of executive functions (e.g., inhibition, working memory updating, task shifting; Friedman & Miyake, 2017). Notably, CC has been variably defined by different authors in the existing literature, but mostly refers to a broad set of top-down executive processes that allows for flexible cognitive adaptation in accordance with current goals (Botvinick & Cohen, 2014). On the other hand, we often referred to FMT power as a possible EEG marker reflecting the need for increased CC (Cavanagh & Frank, 2014), referring to top-down controlled processes exerted by frontal cortical regions. Nevertheless, by no means we intended to fully equate such (need for) CC, as detected during PM in service to behavioral adaptation, with the broader set of executive functions. Moreover, it is important to note that our results concerning FMT are compatible with its putative role in signaling the need for CC, but we did not directly manipulate CC in our experimental paradigms, however. Rather, using the elected gambling task, we mainly manipulated FB valence and expectation across trials, hence investigating PM as the mechanism by which the need for control is possibly elicited, even when not directly instrumental to behavioral performance. This is obviously the case with this task, where participants are invited to guess, bearing in mind that outcome and performance are actually decoupled from each other. Possibly, cognitive processes associated to CC were more clearly recruited during the probabilistic

learning task (chapter 5) than the gambling task (chapters 2-4). As pointed out in chapter 5, both RL and higher level cognitive functions, such as working memory, contribute to learning in humans (Collins & Frank, 2012). Accordingly, FMT power elicited by evaluative FB during a probabilistic learning task may reflect PEs that trigger the need for updating cached stimulus-response associations. Further research is needed to corroborate this last hypothesis.

7. Future Directions

Additional research on reward and motivational processes, as achieved by harnessing the electrophysiology of PM, is absolutely needed, and could follow two main directions.

First, at the methodological level, a number of research avenues could easily spur from some of the main limitations associated with the two experimental designs used in the studies performed and reported in this thesis. We outline some of them hereafter. (I) As outlined in section 4 above, it remains to be better understood how cognitive effort anticipation actually influences preparatory processes at the neurophysiological level, and in particular the recruitment of attention and CC, as possibly reflected by FMT power changes. To this aim, it appears essential to manipulate cognitive effort by means of a specific orthogonal task that more closely taps on canonical features of CC, such as task shifting (Cooper et al., 2019), ideally parametrizing cognitive control demand (Sayalı & Badre, 2019). (II) The advancement of this important research area situated at the crossing of several disciplines in the field would probably greatly benefit from a systematic research line investigating and better specifying which cognitive functions actually elicit robust and reproducible FMT power changes. In particular, cognitive tasks may elicit two types of related FMT signals (Umemoto et al., 2018): a phasic one, elicited at response or FB level and overlapping with canonical ERP signatures of PM (such as the FRN, ERN, N2), and a sustained one, observed during protracted periods of cognitive demanding task execution. The first seems to be more closely associated with the communication of the need for control (Cavanagh & Frank, 2014), while the latter is likely related with sustained mental effort (Hsieh & Ranganath, 2014; Umemoto et al., 2018) and even mental fatigue to some extent (Wascher et al., 2014). A clarification of the functional significance of FMT, as well as the conditions that elicit it, would be highly beneficial for corroborating or disconfirming theoretical and

computational models of PM and ACC function (Alexander & Brown, 2011; Holroyd & Yeung, 2012), as well as implementation models of CC at the neural level (e.g., cortical binding by random theta burst; Verguts, 2017). (III) Here we mostly operationalized motivation as cost-benefit trade-off underlying decision making, and investigated the effect of different forms of cost on reward processing and PM. A following and natural step would be to assess the impact of both expected costs and rewards on motivation, as measured by behavioral performance and decision making about effort exertion (see Vassena, Deraeve, & Alexander, 2019).

Second, at the theoretical level, it appears of utmost importance to further investigate the affective nature of cognitive effort (Inzlicht et al., 2018), with special attention to the modulatory role of specific individual and contextual variables therein (Westbrook et al., 2013). Intriguing open questions, arising from the somehow inconsistent results about the aversive nature of effort (see chapters 3 and 4), are whether I) cognitive effort may be as well perceived as pleasant or desirable, when exerted in a context of low cognitive demand (i.e., the effect of boredom, as experienced in repetitive experimental settings). II) The aversive or valuable role of cognitive effort may be mediated by personality traits, such as the need for cognition (Cacioppo et al., 1996). Considering both the aversive and appetitive sides of cognitive effort will eventually help clarifying its role in motivation and CC, not only in healthy participants, but also in the pathology, including anhedonia. Last, in chapter 5 we observed overall spared RL in MDD, but at the same time, a steeper decrease of FB-locked FMT power over time when learning was hard/impossible, compared to controls. Tentatively, we interpreted this result as reflecting a generally spared core RL mechanism, which is however accompanied by an impaired motivation to maintain adequate levels of CC in MDD. This intriguing dissociation between normal DA-dependent RL and higher level CC impairments in MDD should be further investigated, ideally by parsing working memory from purely RL-based contributions to learning in this

internalizing disorder, as it has been done recently for schizophrenia (Collins, Brown, Gold, Waltz, & Frank, 2014).

8. General Conclusions

In this thesis we employed electrophysiological measures of PM during goal-directed behavior to examine brain mechanisms of reward processing, reinforcement learning, and the influence of effort information therein. Among the most important results reported in this work, (i) we showed that a classical electrophysiological marker of PM and reward processing, namely the RewP ERP component, appears to reflect not only DA-dependent RPE, but also the swift integration of the hedonic value of the FB with effort or cost anticipation, as well as exertion, during PM (chapters 3 and 4). This findings suggests this ERP component may have utility in assessments of the relative contributions of effort avoidance and reward sensitivity to reward processing in healthy participants, but also abnormal reward processing in specific psychopathological conditions, including anhedonia. (ii) Second, we showed that FMT was dissociable from the RewP during PM, and its modulation was consistent with the need for enhanced control over information processing and behavior upon the encounter of an unexpected outcome. Moreover, FMT allowed us to better characterize complex motivational impairments associated with MDD during RL, and more generally PM. In MDD, our new results suggest that the DA-dependent RL is globally spared, but approach motivation, and the ability to sustain CC, are impaired selectively (chapter 5). Taken together, these results corroborate the assumption that PM is a fairly complex mental ability that is underpinned by dissociable neural effects; some closely related to RPE (RewP/FRN ERP component), and others (FMT oscillations) that appear involved in dynamically adjusting levels of CC. This research provided preliminary information about the complex interplay of reward with motivation during PM, as well as how anhedonia and depression may compromise it.

9. References

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Nederlandstalige Samenvatting

Menselijk gedrag wordt gedreven door het nastreven van beloningen. In het dagelijks leven is er echter meestal een kost geassociaeerd met het bereiken van de gewenste doelen, waarbij inspanning vereist is. Dienovereenkomstig vormt de afweging tussen verwachte kosten en baten een fundamenteel aspect van motivatie. Dit proefschrift concentreerde zich op de neurocognitieve basis van beloningverwerking en motivatie bij mensen. De impact van hedonische en motivationele processen, d.w.z. ons vermogen om genoegdoening te ervaren bij en energie te investeren in belonende activiteiten, voor welzijn en productiviteit in ons dagelijks leven wordt vaak onderschat. Stoornissen in deze specifieke domeinen (hedonisme en motivatie) zijn bovendien een kernaspect van psychopathologie die de verschillende diagnostische categorieën overstijgen (Barch, Pagliaccio, & Luking, 2016) en zijn vooral prominent aanwezig in depressieve stoornissen (MDD) (Pizzagalli , 2014).

In dit werk hebben we deze kwesties vanuit een specifieke invalshoek benaderd, namelijk met behulp van elektrofysiologie. Preciezer gezegd, de elektrofysiologie van prestatie monitoring (PM) biedt een tijdsensitief venster op de neurofysiologische mechanismen van beloningverwerking, cognitieve controle (CC) en motivatie. We hebben eerst de functionele significantie onderzocht van standaard elektrofysiologische signaturen van PM, wanneer feedback (FB) de belangrijkste stimulus is die dit proces begeleidt. Ten tweede hebben we van deze markers gebruik gemaakt om neurale mechanismen van beloning en inspanningsintegratie bloot te leggen en hebben we ze benut om de aard en omvang van motivationele stoornissen in MDD tijdens reinforcement learning (RL) te bestuderen. Deze markers van PM omvatten onder andere de beloningspositiviteit (Reward Positivity; RewP), een eventgerelateerde component van het menselijke elektro-encefalogram (EEG) die nauw verbonden is met beloningsgevoeligheid (Proudfit, 2015), evenals oscillerende signalen zoals Frontale Midline Theta (FMT)); dit laatste gericht op de cognitieve tegenhanger van PM (d.w.z. het geeft de behoefte aan verhoogde CC

weer, Cavanagh & Frank, 2014). Na het onderzoeken van de functionele significantie van de FRN / RewP ERP-component in relatie tot de belangrijkste theoretische accounts (hoofdstuk 2), hebben we deze gebruikt om de integratie van beloning met inspanningsinformatie te bestuderen. Een dergelijke integratie is cruciaal voor de kosten / baten-analyse, waarvan motivatieprocessen afhankelijk zijn. Naast het targeten van deze specifieke ERP-marker voor beloningsverwerking op het FB-niveau met een eerder gevalideerde goktaak, hebben we ook gelijktijdige veranderingen die in het gehele EEG-spectrum plaatsvinden en die niet kunnen worden vastgelegd met de standaard ERP-analyse waarop de FRN / RewP is gebaseerd (hoofdstuk 3 en 4). Deze aanpak liet toe om specifieke modulatie in FMT-power te identificeren als een functie van FB-uitkomst en verwachting, die compatibel was met een verrassingssignaal dat de behoefte aan CC weerspiegelde wanneer de uitkomst (FB) afweek van de verwachting. Dienovereenkomstig hebben we FMT-power gebruikt om de motivationele stoornissen tijdens RL in MDD aan te tonen (hoofdstuk 5).

Onder de belangrijkste resultaten die in dit werk zijn gerapporteerd, (i) hebben we aangetoond dat een klassieke elektrofysiologische marker van PM- en beloningsverwerking, namelijk de RewP ERP-component, niet alleen DA-afhankelijke beloningsvoorspellingsfouten (RPE) lijkt te weerspiegelen, maar ook de snelle integratie van de hedonische waarde van de FB met de geanticipeeerde inspanning of kosten tijdens PM (hoofdstukken 3 en 4). Deze ERP-component lijkt dus bijzonder waardevol omdat deze in de toekomst eenvoudig kan worden gebruikt om de relatieve bijdragen van inspanningsvermijding en beloningsgevoeligheid aan beloningsverwerking bij gezonde deelnemers te beoordelen, maar ook abnormale beloningsverwerking in specifieke psychopathologische omstandigheden, waaronder anhedonie. (ii) Ten tweede toonden we ook aan dat FMT tijdens PM gescheiden kon worden van de FRN / RewP en dat de modulatie ervan compatibel was met de behoefte aan verbeterde

controle over informatieverwerking en gedrag na een onverwacht resultaat. Bovendien liet FMT ons toe om complexe motivationele stoornissen geassocieerd met MDD tijdens RL, en meer in het algemeen PM, beter te karakteriseren. Onze nieuwe resultaten suggeren dat in MDD de DA-afhankelijke RL over het algemeen wordt gespaard, maar dat de toenaderingsmotivatie en het vermogen om CC te recruteren selectief beperkt worden (hoofdstuk 5). In zijn geheel bevestigen deze resultaten daarom de aanname dat PM een redelijk complexe mentale vaardigheid is die wordt ondersteund door dissocieerbare neurale effecten; sommige zijn nauw verwant aan RPE (RewP / FRN ERP-component), terwijl andere (FMT-oscillaties) betrokken lijken te zijn bij het op een dynamische manier aanpassen van niveaus van CC.

Data Storage Fact Sheets

In compliance with the UGent standard for research accountability, transparacy and reproducibility, the location of the datasets used in this dissertation are added below. For each of the empirical chapters (i.e., chapters 2 to 5) a separate Data Storage Fact Sheet is completed, detailing which data and analysis files are stored, where they are stored, who has access to the files and who can be contacted in order to request access to the files. In addition, the Data Storage Fact Sheets have been added to my public UGent Biblio account.

% Data Storage Fact Sheet
% Name/identifier study: Dissociable effects of reward and expectancy
% Author: Davide Gheza
% Date: 11 December 2017

1. Contact details
==========
1a. Main researcher

- name: Davide Gheza
- address: Henri Dunantlaan 2, 9000 Gent
- e-mail: gheza.davide@UGent.be
1b. Responsible Staff Member (ZAP)

- name: Prof. dr. Gilles Pourtois
- address: Henri Dunantlaan 2, 9000 Gent
- e-mail: Gilles.Pourtois@UGent.be

2. Information about the datasets to which this sheet applies
==========
* Reference of the publication in which the datasets are reported: Gheza, D., Paul, K., & Pourtois, G. (in press). Dissociable effects of reward and expectancy during evaluative feedback processing revealed by topographic ERP mapping analysis. International Journal of Psychophysiology.
* Which datasets in that publication does this sheet apply to?: the sheet applies to all the data used in the publication

3. Information about the files that have been stored
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3a. Raw data
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* Have the raw data been stored by the main researcher? [X] YES / [ ] NO
If NO, please justify:
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  - [X] other (specify): researcher external hard drive
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* Which other files have been stored?

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- [ ] file(s) that describe the content of the stored files and how this content should be interpreted. Specify:
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% Data Storage Fact Sheet

% Name/identifier study: Integration of reward with cost anticipation during performance monitoring.
% Author: Davide Gheza
% Date: 26 February 2018

1. Contact details
==========
1a. Main researcher

- name: Davide Gheza
- address: Henri Dunantlaan 2, 9000 Gent
- e-mail: gheza.davide@UGent.be
1b. Responsible Staff Member (ZAP)

- name: Prof. dr. Gilles Pourtois
- address: Henri Dunantlaan 2, 9000 Gent
- e-mail: Gilles.Pourtois@UGent.be

2. Information about the datasets to which this sheet applies
==========
* Reference of the publication in which the datasets are reported: Gheza, D., De Raedt, R., Baeken, C., & Pourtois, G. (in press). Integration of reward with cost anticipation during performance monitoring revealed by ERPs and EEG spectral perturbations. NeuroImage.
* Which datasets in that publication does this sheet apply to?: the sheet applies to all the data used in the publication

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* Have the raw data been stored by the main researcher? [X] YES / [ ] NO
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* Who has direct access to the raw data (i.e., without intervention of another person)?
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- [X] file(s) containing analyses. Specify: for each part of the Results section in the paper, a separate .spv or .jasp file is stored with the processed data
- [ ] files(s) containing information about informed consent. Specify:
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Data Storage Fact Sheet for Chapter 4

% Data Storage Fact Sheet

% Name/identifier study: The rewarding effects of cognitive effort avoidance and exertion: an electrophysiological investigation.
% Author: Davide Gheza
% Date: 01 March 2019

1. Contact details
==========
1a. Main researcher

- name: Davide Gheza
- address: Henri Dunantlaan 2, 9000 Gent
- e-mail: gheza.davide@UGent.be
1b. Responsible Staff Member (ZAP)

- name: Prof. dr. Gilles Pourtois
- address: Henri Dunantlaan 2, 9000 Gent
- e-mail: Gilles.Pourtois@UGent.be

2. Information about the datasets to which this sheet applies
==========
* Reference of the publication in which the datasets are reported: Gheza, D., Vassena, E., Baeken, C., De Raedt, R., & Pourtois, G. (submitted). The rewarding effects of cognitive effort avoidance and exertion: an electrophysiological investigation
* Which datasets in that publication does this sheet apply to?: the sheet applies to all the data used in the publication

3. Information about the files that have been stored
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* Have the raw data been stored by the main researcher? [X] YES / [ ] NO
If NO, please justify:
* On which platform are the raw data stored?
  - [X] researcher PC
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  - [X] other (specify): researcher external hard drive

* Who has direct access to the raw data (i.e., without intervention of another person)?
  - [X] main researcher
  - [X] responsible ZAP
  - [ ] all members of the research group
  - [ ] all members of UGent
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  - [ ] other files. Specify:
* On which platform are these other files stored?
  - [X] individual PC
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* Who has direct access to these other files (i.e., without intervention of another person)?
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% Data Storage Fact Sheet

% Name/identifier study: Abnormal approach-related motivation but spared reinforcement learning in MDD.
% Author: Davide Gheza
% Date: 17 January 2019

1. Contact details
==========
1a. Main researcher

- name: Davide Gheza
- address: Henri Dunantlaan 2, 9000 Gent
- e-mail: gheza.davide@UGent.be
1b. Responsible Staff Member (ZAP)

- name: Prof. dr. Gilles Pourtois
- address: Henri Dunantlaan 2, 9000 Gent
- e-mail: Gilles.Pourtois@UGent.be

2. Information about the datasets to which this sheet applies
==========
* Reference of the publication in which the datasets are reported: Gheza, D., Bakic, J., Baeken, C., De Raedt, R., & Pourtois, G. (2019). Abnormal approach-related motivation but spared reinforcement learning in MDD: evidence from fronto-midline Theta oscillations and frontal Alpha asymmetry. Cognitive, Affective, & Behavioral Neuroscience.
* Which datasets in that publication does this sheet apply to?: the sheet applies to all the data used in the publication

3. Information about the files that have been stored
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* Who has direct access to the raw data (i.e., without intervention of another person)?
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3b. Other files

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* Which other files have been stored?
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* On which platform are these other files stored?
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