


FACULTEIT PSYCHOLOGIE EN
PEDAGOGISCHE WETENSCHAPPEN

THE MOTIVATIONAL BRAIN:

NEURAL ENCODING OF REWARD AND EFFORT IN GOAL-DIRECTED BEHAVIOR

Eliana Vassena

Promotor: Prof. Dr. Tom Verguts
Copromotor: Prof. Dr. Wim Fias

Proefschrift ingediend tot het behalen van de academische graad
van Doctor in de Psychologie

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UNIVERSITEIT GENT

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Per aspera, ad astra

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ACKNOWLEDGEMENTS

Per aspera ad astra. This is the opening quote of this book. This latin phrase illustrates the common sense concept according to which the path to great achievements is disseminated with challenges and drawbacks.

This is quite a suitable metaphor for a PhD, a clearly sinusoidal path made of continuous oscillations between very deep lows, and rare but incredibly exciting highs. It's for those highs that the heart of a researcher beats every day, and it's for those highs that I need to thank the people who gave me the opportunity to take part in this journey.

First and foremost, I would like to thank **Tom**, who supervised my work in these 4 years. Since the very beginning, I was impressed by the interest and respect you showed for my ideas and proposals (which as a 1st year enthusiastic PhD student mustn't have been the brightest). You taught me to listen and be prepared to find useful information in any conversation. You taught me the value of ideas, the value of theoretical thinking, the importance of trying to look at the bigger picture. You convinced me of the importance of understanding the underlying mechanisms, by looking at all cognitive processes as emergent properties of the beautifully complex network that the human brain is. I believe that interacting with you incredibly boosted my critical thinking, stimulating me to always try to be one step ahead in any conversation, trying to anticipate your possible (and frequent) objections. You taught me that science is for passionate people, even though my Italian temper might have gone a bit too far on that side. With respect to that, I want to thank you for your patience as well. To sum up, you offered me a great opportunity four years ago, and if I look back, I am so glad I had this chance. These were years of professional and personal

growth, and your contribution to this process, both in terms of mentoring and support, was pivotal. You are a very good scientist, a great mentor, and an excellent person.

The second person I would like to thank is **Massimo**. Se Tom è sempre stato positivo, supportivo e comprensivo, tu hai sempre rappresentato l'estremo opposto. Abbiamo condiviso l'ufficio per tanto tempo, e per i primi due anni non mi rivolgevi quasi la parola. Quando si parlava di scienza, eri ruvido, sarcastico, pungente, talvolta quasi denigratorio. Poi, inspiegabilmente, qualcosa é cambiato, e dietro la corazza del modellista disincantato, è spuntata una persona sensibile, attenta, simpatica e negli ultimi periodi addirittura supportiva ed empatica. Ti ringrazio perchè da subito mi hai insegnato a combattere. Mi hai insegnato che le idee hanno valore, ma vanno difese. Mi hai insegnato, forse alla maniera accademca piú tipicamente italiana, che la ricerca è un mondo difficile, spesso impietoso e porta grandi sofferenze. Ma mi hai anche mostrato che questo prezzo si paga con il cuore, ed il ritorno rimane incommensurabile. So che negherai leggendo questa frase, ma questo tipo di passione traspare ogni giorno dai tuoi occhi.

Many other people walked side by side with me during this journey.

Wim, I would like to thank you for being my copromoter. You always had sharp and useful comments, while setting up new projects, discussing results or writing them up. You always had that critical thinking that is so crucial at many stages of our work. On top of that, you were very kind and supportive during difficult moments, when I was having a hard time with publishing.

Ruth, you helped me so many times that probably thanking is not enough. In fact, I still owe you a dinner! You were always ready to answer to all my questions, helping me with analyses, and supporting me through the peer-review (rejection) process. You kept my interest for neuroimaging alive also in the most difficult moments. Moreover, you are such a pleasant and kind person. Having you as colleague and friend is really a pleasure.

Nico, thanks for participating and supporting me during my "brainstem struggle". I knocked on your door so many times, and I would always come out with solutions, tips and really useful insights. Thanks for helping me so much with the first article as well. I really learned a lot.

Gilles, thank you for your enthusiasm, support and positivity. As a member of my guidance committee, you provided extremely useful comments and insights. As a person, every time I talked to you I felt completely enthusiastic about whatever results, projects or even just ideas. Such an attitude is rare, and I really admire you for that.

Marcel, as a member of my guidance committee I would like to thank you for always providing a different perspective on things. At every meeting you were able to point out a part of my results that I had overlooked, a possible interpretation that I didn't consider, as well as interesting ideas for new analysis and new projects. That was extremely helpful at many stages.

Another person I need to thank is **Matt**. The collaboration we started is so interesting and productive. You gave me the chance to visit you in Princeton and to get in touch with a wonderfully stimulating environment.

A special thought goes to my bachelor and master thesis supervisor. **Luisa**, devo ringraziarti per aver destato il mio interesse nei confronti delle neuroscienze, e per avermi incoraggiato a venire a Gent. Questa esperienza

resterà per sempre preziosa ed indimenticabile, e senza il tuo aiuto non sarebbe stata possibile. Grazie di cuore.

During these years, support also came from my lab-mates, with whom we shared lab-meetings, lab-drinks and a lab-trip, where science was always dominating in every conversation (even during the traditional dances party in the Ardennes). Massimo, I've already thanked you, so no room for you here. **Marlies**, we started together and you just left, heading towards a new and exciting experience. Thanks for the chats, the support and for being always so kind and understanding. **Filip**, your sharp comments were always really valuable, and the combination with your wit often made them outstanding. Good luck with your new and exciting job at the most advanced research facility in Belgium (the ULB obviously!). **Seppe**, you are no longer one of us, but it was really nice to meet you and since you left, nobody could fill the void in the lab. We still miss you! **Anand**, you also took off for new challenges. In the last years I came to know you as the sincere, caring and kind person you are. I wish you the best of luck with your next steps. In bocca al lupo! **Clio**, you are very skilled, hard worker and such a sweet person. It's always fun to have a chat with you. **Esther**, you are so driven and motivated (perhaps a little too much ☺). This really impressed me. Keep your passion and ambition, and you will see, it will pay off.

Outside the lab, I had the chance to meet many other great colleagues, with whom I shared at least past of this experience. **Clémence**, you work and live in Lille now, and you have a beautiful family. I'm so happy for you. It was a pleasure to meet you and to have you as a friend. **Egbert**, you also continued somewhere else your successful career as a researcher, and now as a daddy. I haven't forgotten how much you helped me in the early stages, and I really want to thank you for that. **Senne**, it now feels like ages ago, but

thank you so much for housing me when the roof literally fell down on me in my first room in Ghent. Besides, thanks for always being kind and helpful. **Nathalie** and **Wout**, thank you for the chats and for helping me many times with all sorts of things. **Femke**, you took a different path, but for the time we were colleagues I really appreciated meeting you and talking to you.

Hanna, I'm going to thank you as a colleague, but especially as a friend. Basically you erased the negative prejudices I had towards Dutch people (probably produced by leaving in Flanders? ☺) and you showed me the great person you are. Despite your blonde hair (of which I'm kind of jealous anyway) you are such a smart, sweet and fun girl. I'm really happy I met you and I hope we can keep in touch for a long time. **Hanne** and **Uschi**, chatting and hanging out with you is always fun. You also helped me when I was having a hard time for personal problems, and for that you deserve a sincere thank you. **Lize**, we started our PhD together, and shared nice and difficult moments. Thanks for being helpful, kind and available. **Maggie**, we also started together and both our lives changed a lot since the beginning. You are a sweet person and I wish you the best of luck for the PhD and for the next steps. **Paul**, you arrived just a few months later, and it was very nice to meet you and spend some time with you. I also need to thank several other colleagues, who listened to my complaints, supported me in difficult times and celebrated with me afterwards. Among these people, a special thanks goes to **Mario** (now a daddy, congrats!), **Lara** (the TMS/Tdcs/Tpj/MEP expert), **Davide** (free will will conquer the world), **Jelle** (that experiment is waiting for us), **Elger** (no, I don't have any new publications, and therefore my career is in jeopardy), **Chiara** (stai ancora smoccolando sui render?), **Carsten** (are you going to the gym? My friend, let's just have a beer), Toru (uhhhhhh, that jenever was strong), **Zachary** (I still don't understand half of

the things you say, but you seem nice), **Oliver** (stop going back to Switzerland, we need you here), **Dimitris** (spinakotiropitaki), **Maarten**, **Joris**, **Jean-Philippe**, **Durk**, **Michel**, **Pawel**, **Raquel, Muhammet** and **Linde**.

A special thanks goes to **Christophe**, for always helping me with any sort of problem. You are really the most precious colleague! Sorry for always filling up the workstation! A very special thanks goes to **Lies**. As I had the chance to tell you before, you are the most awesome problem solver I've ever met. Sorry for bothering you so often with the excuse of not being a native Dutch speaker, and thank you so much for helping me basically with everything! A very very special thanks goes to **Pieter**, who always helps me at the scanner (despite blaming my Italian temper for the overwarming problems of the machine).

One last special thanks goes to **William H**, who gave me opportunity to stay in Gent for a little longer. I'm looking forward to all the new projects and challenges.

Next to these geweldige collega's, I was so lucky to be supported by valuable friends. **Lien**, we have known each other for a bit longer than one year, but lately you really became like a little sister. Thank you for your support during the stressful period of thesis writing. That was incredibly appreciated and helpful. I hope I will be able to do the same for you. **Iemke**, my twirling-fairy roommate: we are having such a great time living together. Moving to our apartment and moving in with you was one of the best choices. Thanks for being fun, for the nice chats, and for taking care of me like a mum sometimes. **Marit**, we haven't known each other for a long time, but you are such a sweet person and you already helped me so many times Thanks for being so kind and helpful. **Marijke**, I'm so glad I attended that

statistics course where we met. You are a beautiful person, my friend, and now a beautiful mom. I really want to thank you for being such a great friend, always kind and helpful. Some credit also goes to your lucky husband **Wim** obviously. **Helena** and **Roxana**, you were in Ghent only during the first year of my PhD, but we had such a great time and I know we can count on each other. I hope to see you soon girls. **Roma**, you are really an example to me. You are one of the brightest and at the same time sweetest people I know. You manage to be a successful scientist and a lovely and caring mom. I really admire you and I wish I could manage to follow your steps. **Igor**, you just defended your thesis and you did great. Despite knowing you for a long time, we got closer only lately. You are a very nice person, and a brilliant and driven researcher. Thanks for your support. I have to address a special thanks to the friends I had the luck to find at Dutch class. **Fabrizio**, tutto e' cominciato con scroccarti vari passaggi per raggiungere la lontanissima scuola Het Perspectief. Chi l'avrebbe detto che avrei imparato ad apprezzarti tanto. Anche tu ti sei imbarcato in una nuova sfida, per cui ti auguro un sincero in bocca al lupo. Sono certa che raggiungerei ogni obiettivo, ed mi renderai fiera. Ci manchi, e non vediamo l'ora di vederti in Sicilia. **Marianna** (Mariantje + 2), mi sei stata incredibilmente vicina nel periodo piu' difficile, proprio in queste ultime settimane. Il valore di questo supporto e' stato davvero inestimabile. Grazie a te, ed al tuo dolcissimo marito, **Jacopo**, anch'egli un amico insostituibile. In bocca al lupo ad entrambi per le molteplici avventure che si delineano all'orizzonte. **Katty**, I really admired you enthusiasm and working (and also working out!) with you was really exciting.

Inoltre un pensiero di ringraziamento va ai miei amici in Italia. **Ilenia**, non ci sentiamo spesso per ovvie ragioni, ma ti ringrazio per essermi sempre

vicina. **Marco**, sei sempre nei miei pensieri e spero di vederti presto. **Federica**, sei una cara e sincera amica. Nonostante la lontananza, sappi che puoi contare su di me. **Clara**, le nostre strade si sono un po' allontanate, ma resterai sempre una cara amica per me.

The biggest thank you however, has to go to my family. **Mamma e papà**, mi avete sempre sostenuto, in tutte le mie scelte. Mi avete appoggiata, incoraggiata, ascoltata, ed all'occorrenza abbracciata. Tutto questo non sarebbe stato possibile senza di voi, che siete sempre stati la mia motivazione primaria. L'incentivo più grande è sempre stato il desiderio di sorprendervi, e rendervi orgogliosi di me. Non deve essere facile vedere una figlia partire, e poterla rivedere solo per pochi giorni ogni tre o quattro mesi. Per tutto quello che avete fatto, ed ancora fate per me, vi ringrazio immensamente. **Mamma**, tu sei veramente la mamma piú dolce del mondo. Spero un giorno, di poter a mia volta essere una madre come tu lo sei stata per me. Per questo motivo, questa tesi è dedicata a te. **Papà**, penso di aver preso da te il coraggio e l'ostinazione: senza queste qualità, non avrei mai potuto raggiungere questo obiettivo. **Arianna**, più che una sorella ti ho sempre considerata un angelo. Sei una ragazza dolcissima, intelligente, una vera amica. Fin da quero eri piccola, un tuo sguardo mi rincuorava ed aiutava più di ogni parola, supportandomi nell'affrontare qualsiasi difficoltá. Grazie per tutto ciò che mi hai dato ed ancora mi dai. Ricordati che ci sono e ci sarò sempre. Anche se fisicamente siamo lontane, sei sempre nei miei pensieri e nel mio cuore. **Nonna**, devo assolutamente ringraziare anche te. Mi hai praticamente cresciuta, e ho sempre provato per te una profonda ammirazione. Hai avuto molte difficoltá nella tua vita, ed ora finalmente tanti meritati riconoscimenti. Penso di avere il tuo carattere. Tu stessa dici sempre che dalla fronte al mento, assomiglio proprio a te. Sei una donna

formidabile, e spero con tutte le mie forze di seguire il tuo esempio. Un grazie sentito anche alla mia zietta **Lilli**, a mia zia **Adel**e e alla mia cuginetta **Chiara**.

Bedankt ook aan mijn andere familie. **Sjany**, je bent altijd zo lief. Ik voel het echt dat ik een tweede moeder heb, en darvoor hartelijk bedankt. **Marieke**, **Dirk-Jan**, **Paul** en **Renske**, het is altijd leuk om jullie te bezoeken. Jullie zijn allemaal zo lief en aardig. Bedankt!

As you suggested yourself, the best comes at the end. So, now it's your turn. Grazie **Marinus**. Amore mio, you are the true engine behind this thesis. In bad times and good times you were always at my side. We met two years and half ago, randomly, at a bus stop. That was the best random thing that ever happened to me. You are a beautiful person. You are smart, sweet, caring and understanding. You were hugging me and having good words for me when I was doubting myself. You were looking at me in the eyes, telling me you had no doubt I was going to make it. When good times came, you were there with me to celebrate, showing how proud you were of me and how happy you were for me. To me, you are a boyfriend, a friend and a family altogether. Having a person like you in my life, it's just geweldig.

I started this book with a quote about how the pathway to great achievements, to the stars, is full of challenges. Even though they feel a bit closer now, stars are still far away. However, isn't the journey what really matters?

Grazie a tutti. Thanks everyone. Bedankt allemaal

Eliana

CHAPTER 1
INTRODUCTION

"Human behavior flows from three main sources: desire, emotion and knowledge"

Plato, The republic, ~380 BCE

The idea that motivation constitutes the primary engine of human behavior dates back at least to ancient Greece, where the philosopher Plato assigned to "desire" a cardinal role in his theory of soul. This component was also described as appetite, which encompasses a number of basic human urges, from hunger to sexual needs, as well other non-biological goals which entail pleasure, like money, political activity or even physical exercise (Wagner, 2001). In this perspective, appetite was considered as a strong driver of human behavior, independent of reason and possibly interfering with rational behavior.

Since this early intuition, the study of motivation has evolved across multiple theories, constructs and applications, capturing the interest of several disciplines, like philosophy, psychology, economics and more recently neuroscience and machine learning (Rangel, Camerer, & Montague, 2008). The scope of this dissertation embraces the most recent steps of these developments, with a particular focus: how motivational drive is embedded in the human brain, and how this shapes adaptive behavior.

THE QUEST FOR VALUE

The study of motivation relies on the principle that animals' behavior is guided by the pursuit of extrinsic or intrinsic benefits, such as rewards, pleasure and satisfaction (Berridge, 2004). Pursuing benefits requires the ability to track benefits, their probability of occurrence, and possibly other associated features (e.g., costs). In the literature, the term *value* is used to indicate how such features are combined. Classic decision theory posits that expected value of an option or object is an additive function of its possible reward outcomes, each outcome weighted by its probability of occurrence. This influential concept was formulated in the 17th century by the mathematician and philosopher Blaise Pascal and dominated economic models for two centuries (Schoemaker, 1982). In 1979, Kahneman and Tversky expanded this idea, by formulating the prospect theory. This theory postulates that the value of an option or object is also influenced by contextual and cognitive factors, which shift a reference point. As a result, value may vary depending on the circumstances and on the state of the agent. This theory succeeded in predicting a number of human behaviors, deviating from the classic decision theory predictions, and gave a strong impulse to the cross-disciplinary investigation of value-based decision making (D'Acremont & Bossaerts, 2008; Glöckner & Pachur, 2012; Rangel et al., 2008; Takahashi, 2012; Trepel, Fox, & Poldrack, 2005).

The influence of value on behavior has been investigated focusing on two types of rewards. On the one hand, some objects are endowed with intrinsically rewarding properties, as they respond to human adaptive needs, such as food. These rewards are called primary reinforcers. In other words, these objects are intrinsically appetitive, which means they elicit approach behavior. On the other hand, such a value can also be attributed to a neutral

stimulus, via learning. A long tradition of behavioral experiments in animals described the phenomenon of *conditioning* (Skinner, 1953) which implies that a neutral stimulus can be assigned with a rewarding value, when this stimulus predicts a reward. This line of research gave a substantial contribution to the understanding of learning mechanisms which occur in presence of reward, with or without action, in a simple or complex context and with or without punishment. What is relevant to the current work, is that this laid the basis for *reinforcement learning* theories (learning via reinforcements, that is the receipt of a reward, Rescorla & Wagner, 1972; Sutton & Barto, 1998) and their application to animal and human behavior. These theories provided a promising framework for understanding how value drives adaptive behavior (Matthew M Botvinick, Niv, & Barto, 2009; Maia, 2009).

Neural correlates of value and reward prediction

The neural correlates of value have been investigated since the 20th century. In 1954, Olds and Milner showed that electrical stimulation of specific brain region in rats had rewarding properties. If given the chance of controlling the stimulation, the animals would keep on self-delivering the stimulation. Subsequent studies determined that these regions were part of the dopaminergic (DA) network, including the Ventral Tegmental Area (VTA) and the nucleus Accumbens (nAcc, Corbett & Wise, 1980; Phillips, Brooke, & Fibiger, 1975).

Since then, studies have proliferated trying to determine how value and reward-related behavior might be associated with this neural substrate.

In a seminal study in 1998, Schultz showed that VTA can actually encode not only reward receipt, but also reward prediction (Figure 1).

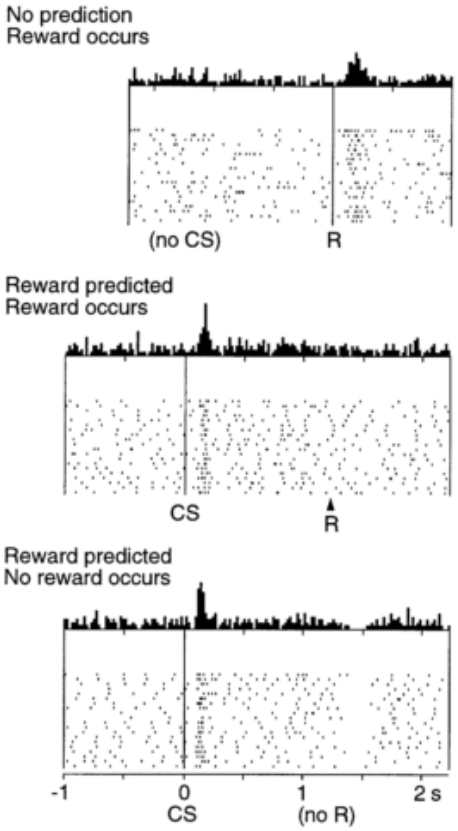

Figure 1: Recordings from dopaminergic (DA) neurons in the VTA. The top graph represents DA firing at reward receipt, when no prediction was formulated. The middle graph shows DA firing when the reward predicting stimulus (conditioned stimulus CS) occurs. This illustrates the DA shift, as no response is detected at reward receipt (R). The bottom graph shows DA firing pattern in presence of a violation of the prediction: CS predicts a reward, and this is associated with increased firing; no reward is delivered (no R), and this results in a drop in DA firing (adapted from Schultz, 1998).

When a stimulus is reliably associated with a reward, the firing of VTA neurons is initially coupled with reward delivery, but then shifts to the predictive stimulus instead. In other words, VTA-DA neurons encode the expectation of the reward. This phenomenon is often referred to as dopaminergic shift. Furthermore, the same neurons fire when the experienced outcome diverges from the learned prediction. This signal is named prediction error, and can encode both a positive and a negative violation of the expectation (positive prediction error and negative prediction error, respectively). These findings opened the way to a conjoint research effort across the fields of neurophysiology, neurobiology and psychology to determine how VTA-DA input to cortical and subcortical brain areas contributes to neural encoding of value and reward prediction.

VTA-DA input reaches a widespread cortico-subcortical network (Figure 2). Direct targets are for example the ventral and dorsal striatum, the Nucleus Accumbens (NAcc), the hippocampus, the amygdala and the medial Prefrontal Cortex (mPFC, Haber & Knutson, 2010; Lisman & Grace, 2005). All the nodes in this network have been shown to contribute to reward-related behavior in humans in a wealth of studies using functional neuroimaging (Knutson & Cooper, 2005; Liu, Hairston, Schrier, & Fan, 2011; Rangel & Hare, 2010; Vassena, Krebs, Silvetti, Fias, & Verguts, 2014).

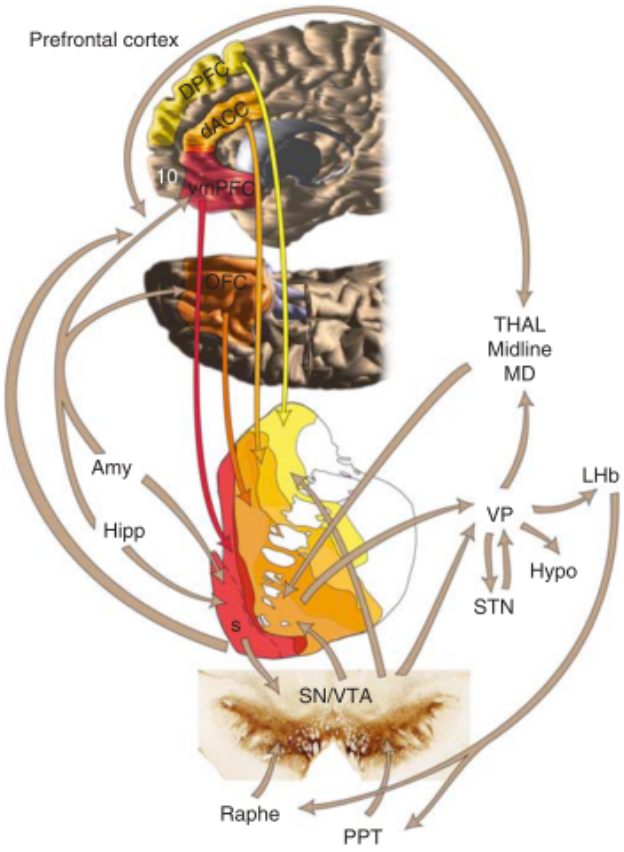

Figure 2: Schematic illustration of the reward circuit and the pathways linking the different regions. The bottom part represents the brainstem, with Ventral Tegmental Area (VTA), Substantia Nigra (SN), Raphe nucleus and Pedunculupontine Nucleus (PPN). The central structure represents Nucleus Accumbens (NAcc), part of the Ventral Striatum, where s is a specific part of the NAcc, called shell. On the top of the figure, the cortical targets are represented: Dorsolateral Prefrontal Cortex (DLPFC), dorsal Anterior Cingulate Cortex (dACC), and ventromedial Prefrontal Cortex (vmPFC). On the sides, other interconnected structures are represented, with respective projections: Amygdala (Amy), Hippocampus (Hipp), Thalamus (Thal), Ventral Pallidum (VP), Subthalamic Nucleus (STN), Lateral Habenula (LHb), and Hypothalamus (Hypo, adapted from Haber & Knutson, 2010).

The ventral striatum (including the nucleus Accumbens) plays a pivotal role in appetitive behavior, encoding value at reward delivery and driving value-based learning (Diekhof, Kaps, Falkai, & Gruber, 2012). Striatal activation typically correlates with individual preferences and with the value attributed by subjects to a specific stimulus (Berridge, Robinson, & Aldridge, 2010; Kringelbach & Berridge, 2009; Levy & Glimcher, 2011; Sabatinelli, Bradley, Lang, Costa, & Versace, 2007). The mPFC has also been implicated in different aspects of value processing, including reward prediction and outcome value coding. However the functional architecture within the mPFC remains debated. One main question concerns the hypothesis of a functional segregation of value coding and reward prediction coding across the main sub-regions, that is the Anterior Cingulate Cortex (ACC) and the ventromedial Prefrontal Cortex (vmPFC, Rushworth, Behrens, Rudebeck, & Walton, 2007).

Computational accounts of value and reward prediction

The dopaminergic shift and prediction error coding in the VTA demonstrated by Schultz (1998) inspired fruitful computational work, aimed at gaining a mechanistic understanding of value-based neural computations. Montague, Dayan, and Sejnowski (1996) exploited the principles of Reinforcement Learning (RL, Sutton & Barto, 1998) to model VTA dopaminergic signaling. Specifically, they formulated the Temporal Difference (TD) reinforcement learning algorithm. This model formalizes the concepts of reward prediction as a value that is updated over time on the basis of experienced outcomes. Strikingly, this model succeeded in simulating both dopaminergic shift and prediction error signals, giving rise

to a wealth of studies applying RL principles to investigate value-based learning and decision-making (Garrison, Erdeniz, & Done, 2013). Building on this foundation, recent work focused on bridging the gap between single-neuron simulation and higher level cognitive effects (Alexander & Brown, 2011; Silvetti, Seurinck, & Verguts, 2011). For example, Silvetti and colleagues implemented the Reward Value and Prediction Model (RVPM, Figure 3). This model simulates meso-limbic interactions borrowing the actor-critic architecture in the RL framework (Sutton & Barto, 1998). Put simply, the critic is the unit that stores value information associated to a certain stimulus, which is updated on the basis of outcomes to formulate future predictions similarly to previous computational RL models (Sutton Barto, Montague, Dayan, & Sejnowski, 1996). The authors also formulate a neurobiologically plausible architecture, hypothesizing the critic functions to be implemented in the ACC. The innovative contribution of RVPM resides in its ability of simulating a number of higher level well-known cognitive effects, including response conflict (Botvinick, Cohen, & Carter, 2004; van Veen, Cohen, Botvinick, Stenger, & Carter, 2001) and volatility effects (Behrens, Woolrich, Walton, & Rushworth, 2007) in the ACC. Importantly, these effects arise from the behavior of the model, without explicit implementation of conflict and volatility. The model also accommodates a number of previous fMRI results, and in a later model-based fMRI study the same authors demonstrated the role of mPFC (especially the ACC) in encoding reward prediction error (Silvetti, Seurinck, & Verguts, 2013). This work provides a framework to study value-based goal-directed behavior (Silvetti, Alexander, Verguts, & Brown, 2013), also in pathological conditions where DA signaling is impaired (Silvetti, Wiersema, Sonuga-Barke, & Verguts, 2013).

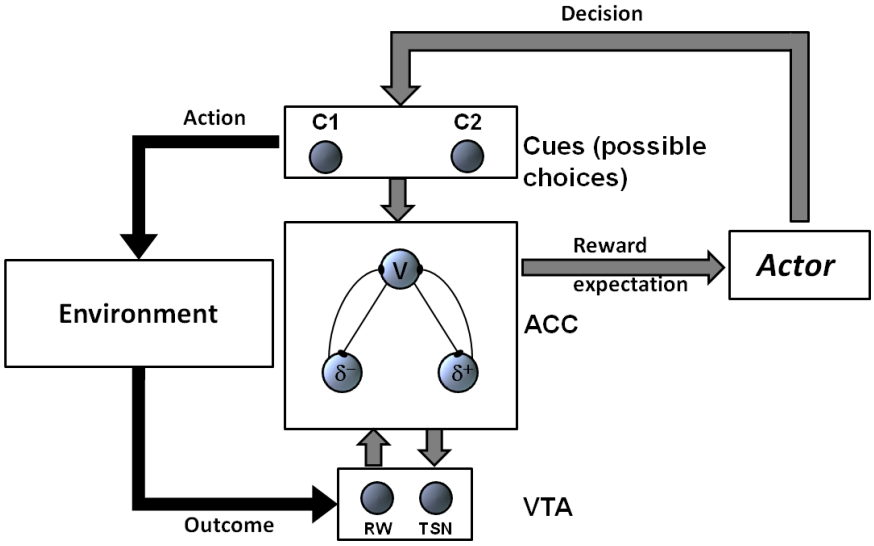

Figure 3: Reward Value and Prediction Model (RVPM). C1 and C2 represent the possible stimuli to choose among. Every choice is associated with an action producing an effect on the environment. This results in an outcome, evaluated via dopaminergic VTA input, which provides ACC with a reward signal (RW) and a temporal difference signal (TSN), reproducing the dopaminergic shift effect. In the ACC module, value *V* is represented, together with δ units. δ+ units encode positive violations of the predicted reward (positive prediction errors). δ- encode negative violations of the predicted reward (negative prediction errors). On the basis of environmental outcomes, ACC computes new expectations, leading to new choices (adapted from Silvetti et al. 2013).

BEYOND VALUE: WHEN REWARD COMES AT A COST

Despite the substantial role played by value in motivating goal-directed behavior, this construct alone does not exhaustively address all real life situations. In a natural environment outside the laboratory setting, earning a benefit usually entails some cost. For example, the benefit of a wage only comes in exchange of a month of a hard work. The breathtaking view from the summit of a mountain requires hours of effortful climbing. As a more ancestral example, a predator will have his dinner served only upon running after (and faster than) his prey. Clearly, pursuing a reward often requires a certain amount of effort. Not surprisingly, this exerts a powerful influence on decision-making behavior and motivation in a number of contexts.

In 1989, the social psychologist Jack Brehm defined motivation itself as the amount of effort one is willing to exert to achieve a goal, such as the receipt of a reward (Brehm & Self, 1989). More specifically, in Brehm's theory, motivation is the result of a joint function of potential motivation (need, outcome value) and the difficulty of the required behavior. From then on, the relationship between potential reward and effort implied in obtaining it, received considerable attention in economics. For example, in the labor-supply theory (Nicholson & Snyder, 2012) value is represented as a utility function combining amount of work, wage and extra unearned compensations. Interestingly, this framework powerfully predicts apparently irrational human behaviors, such as the effect of an income-compensated wage decrease. When workers are given a non-earned payment upfront, but their wage (earned income) is reduced, they will choose to work less, even if

by working the same number of hours as before they would have managed to reach the same total amount of money.

To sum up, motivation sustaining effortful behavior has been mostly investigated in the field of economics and social psychology. Only recently cognitive psychologists became interested in this topic, discovering the applicability of previous theories to a wider range of behaviors, also outside the working environment. Kool and Botvinick for example (2012), replicated the income-compensated wage decrease effect in laboratory settings, when the involved factors were candies, as a reward for performing cognitively demanding tasks. These authors also discuss the application of the labor-supply theory in the broader perspective of decision-making. This cross-disciplinary evidence provides empirical support for the intuition that humans estimate the effort involved in the pursuit of a certain appetitive goal, and that this shapes their decisions.

Neural correlates of effort estimation

If required effort influences behavior as a function of attainable reward, prospective effort needs to be encoded by the brain as reward is. The first evidence for this claim comes from animal research. Salamone and colleagues showed in several studies that dopaminergic neurotransmission is essential in this process (Cousins, Atherton, Turner, & Salamone, 1996; Salamone, Correa, Farrar, & Mingote, 2007; Salamone, Correa, Mingote, & Weber, 2005; Salamone, Correa, Nunes, Randall, & Pardo, 2012). Animals show effort avoidance, unless effort exertion leads to a reward. In that case, more effort is exerted as a function of available reward. However, this effort-overcoming behavior is impaired if DA structures are lesioned or if DA

levels are pharmacologically depleted. This has been shown in a T-maze setting: control rats would normally choose to climb a barrier when this would lead to higher amount of food. DA-impaired rats however, would choose the easier (no-barrier) less rewarding option instead.

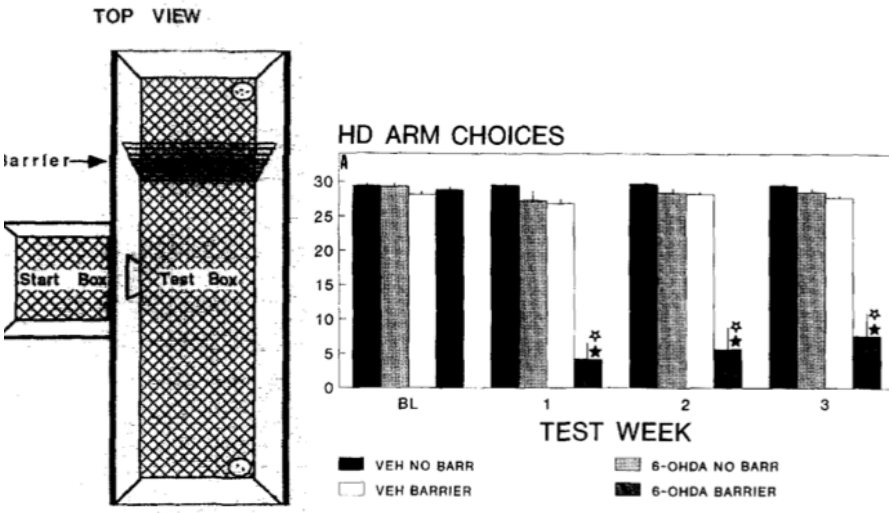

Figure 4: On the left, the typical T-maze setting. The animal is placed in the start box. When the trial starts, the animal can choose to go to the left (high density arm), where more food will be available, but the animal must climb over a barrier. Going to right offers a lower amount of food, but no (climbing) effort is required. On the right, behavioral results are reported, with on the y axis the number of choices for the high effort/high reward arm. Importantly, when striatal dopamine is impaired via 6-hydroxidopamine lesion, the number of choices for the high effort/high reward arm drops dramatically (right panel, 4th column in each test week, adapted from Salamone et al. 1984).

This evidence that DA network is essential in supporting effortful behavior received support from neuropsychological studies in humans. Patients with a mesio-frontal lesion (including the mPFC) show a deficit in initiating motivated behavior. Moreover, depressed patients, known to have DA-alterations, show decreased willingness to exert effort in exchange for rewards as compared to controls (Treadway, Bossaller, Shelton, & Zald, 2012). This indirect evidence in humans is backed up by experimental studies investigating the correlates of effort estimation with fMRI. Some studies report a crucial contribution of the ventral striatum and the ACC in effort-discounting tasks (Botvinick, Huffstetler, & McGuire, 2009; Croxson, Walton, O'Reilly, Behrens, & Rushworth, 2009). In such tasks, participants are confronted with different rewards, entailing different amount of efforts. Apparently, the value of the prospective reward is *discounted* (i.e. decreased) by the amount of effort implied in obtaining it, thus resulting a *net-value* signal. This net-value signal would then drive choice adaptively. However, contrasting perspectives remains on how prospective effort is *anticipated* (i.e. estimated in advance), especially concerning its direct encoding by the ACC and striatum, and how this is linked to effort-related decision-making and preparation for effort exertion.

Computational accounts of effort estimation

The wealth of results from animal research stimulated a mechanistic understanding of effort estimation and exertion via computational modeling. A first interesting model was proposed by Niv, Daw, Joel and Dayan (2007), who operationalized effort coding as a combination of a vigor cost and an opportunity cost. The vigor cost was associated with energizing behavior,

that is initiating an action. The opportunity cost referred to the worth of allocating a certain amount of time to a specific task, thus avoiding alternative tasks. Hence, value resulted from a combination of reward and the two related costs. However, this model was specifically applied to physical effort, thus without considering possible influence of cognitive factors. Moreover, the model did not account for difference in effort allocation in other dimensions than time (e.g., allocating attention).

Recently, a new theoretical framework has been proposed, which has the potential to go beyond this limitation. Shenhav, Botvinick and Cohen (2013) incorporated effort cost in the computation of value, postulating that the brain estimates the value of exerting *control,* in terms of cognitive effort. In other words, exerting effort is valuable as it leads to a reward. This type of encoding would allow overcoming the otherwise aversive effort, but only when this is considered worth. This new theoretical perspective opens interesting computational possibilities, and calls for a better specified functional understanding of effort anticipation.

OUTLINE OF THE DISSERTATION

As emerged from the overview in this introduction, some crucial questions are left open with respect to the neural basis of reward prediction, value encoding and effort anticipation. The goal of this dissertation was to tackle these issues, using functional Magnetic Resonance Imaging (fMRI) and Transcranial Magnetic Stimulation (TMS) as neuroscientific tools for investigating the architecture of motivation.

As a first step, we addressed the neural representation of value and reward prediction, coupled with decision-making. In **Chapter 2**, we discuss

the debate concerning the functional specialization within mPFC. This region is clearly implicated in both value coding and reward prediction (Rushworth & Behrens, 2008). Hypotheses of functional segregation have been put forth, with respect to two sub-regions of mPFC, namely vmPFC and ACC. These hypotheses suggested a primary role for vmPFC in value coding (Grabenhorst & Rolls, 2011) and a primary role of ACC in reward prediction (and prediction error, Alexander & Brown, 2011; Silvetti, Seurinck, & Verguts, 2011). However, this had never been systematically tested in the same experimental settings in the same subjects. The goal of this chapter was to investigate this hypothesis. Moreover, the potential influence of decision-making processes on value coding and reward prediction had never been questioned. This additional experimental question was integrated in the design, aiming at better profiling the mPFC functional architecture. This region is indeed implicated in choice and action selection (Brass & Haggard, 2007; Forstmann, Brass, Koch, & von Cramon, 2006). To address these questions, a gambling paradigm was implemented, where participants could choose between a gamble and a sure (but smaller) win. Participants were exposed to two types of gamble, a risky one (low probability, high payoff) and a safe one (high probability, low payoff). This allowed to target reward prediction and prediction error coding, as in a number of cases the outcome would be unpredicted. On top of this, in half of the trials, a forced choice was imposed, thus targeting the specific influence of free vs. imposed choice on value and reward prediction coding. This experimental design provided the opportunity to investigate one additional question on the same dataset, namely the neural underpinnings of individual differences in risky choice behavior. This is reported in the Appendix to **Chapter 2**, where we show that risk preference is associated with decreased anterior Insula activation during gambling, supporting the role of this area

not only in risk estimation (Singer, Critchley, & Preuschoff, 2009), but also in explaining inter-individual variability in risky choice.

After clarifying the neural underpinnings of value and reward prediction, we moved to the next step, that is the neural representation of costs. In **Chapter 3,** we implemented an fMRI paradigm investigating the anticipation of a specific cost, *cognitive effort.* This cost was chosen for its central role in motivated behavior, and for its ubiquity in everyday life, as well as in typical experimental settings. Specifically, we targeted the anticipation of effort, comparing it with the anticipation of a reward. Importantly, the delay confound was controlled, keeping execution time constant across easy and hard effort levels. In this experiment, we showed that anticipation of higher effort and greater reward is associated with activation of the same cortico-subcortical network, involving ACC and striatum. This network seems to support engagement towards successful task completion, resulting in reward delivery, thus suggesting a motivational role for these regions. Despite the convergence with recent fMRI as well as neuropsychological evidence (Devinsky, Morrell, & Vogt, 1995; Németh, Hegedüs, & Molnár, 1988), this result stands against the dominant *net-value account* of ACC function (Amiez, Joseph, & Procyk, 2006; Rushworth & Behrens, 2008; Silvetti et al., 2011). According to this theory, these regions encode the net value associated with a specific stimulus, that is the attainable reward discounted by the cost (in our case effort). One clear prediction arising from this framework is that higher net value would be associated with higher ACC activation, and vice-versa lower net value (deriving from higher cost) would be associated with lower activation. Our results however, showed that anticipating a higher effort elicited increased activation, thus

seemingly incompatible with a net value perspective, and instead more compatible with a motivational coding.

The result from Chapter 3 called for further investigation of neural encoding of effort, with special attention to the role of ACC in this process. Disentangling this issue was the goal of **Chapter 4**. In this fMRI experiment, we aimed at identifying effort encoding type, directly contrasting the hypothesis of net value coding against the hypothesis of a motivational coding. A first crucial point characterizing previous studies was that decision-making processes were not controlled for. In fact, ACC is involved in action selection and decision-making (Brass & Haggard, 2007). However, studies investigating anticipation of value and effort did not systematically control for this factor. Some studies presented cues to the subjects, associated with upcoming, and unavoidable, effortful and rewarding tasks. Other studies involved the possibility for the subjects to choose effortful and rewarding tasks, according to their own preference. ACC has been associated with both anticipation of effort when no choice is required, as well as with decision-making situations (both involving effort and not), and therefore considering this factor is crucial. However the role of decision-making was never investigated systematically in the same setting with the same participants, thus preventing from pinpointing specific contributions of ACC to the different processes. Our paradigm was design to answer these needs. We implemented an fMRI task where participants were confronted with some cues, each proposing a combination of prospective effort and potential reward. In a first phase, they would see all these cues, and choose which one they were willing to accept (in comparison with a baseline cue). The accepted cues would then come back in a second phase, associated with a cognitive task, entailing the selected effort and potentially

granting the announced reward upon correct completion. This allowed to simultaneously target the type of encoding (net value vs. motivational), and the influence of decision-making on this encoding. Additionally, effort was manipulated parametrically across four different levels, thus providing finer-grained information. As a result, we showed that ACC supports effort encoding during both effort-related decision making as well as during anticipation of effortful performance. We also show how this is modulated by phase, showing that during decision-making parametric encoding of effort is better explained by a quadratic trend. This is particularly relevant, as it seems to be consistent with the previously illustrated theoretical account of ACC function, formulated by Shenhav et al. (2013). These authors suggested indeed that the ACC computes the value of allocating a certain amount of cognitive resources to pursue a certain goal. In fact, this might go beyond the dichotomy between net value coding and motivational coding, as ACC might be integrating both effort and value information, including the value of exerting the required effort, as it leads to a final reward. As a results, ACC activity seems to support goal-directed (reward-driven) behavior, both in estimating value and sustain effortful actions towards the goal. The importance of this result resides in its ability to provide a framework that reconciles seemingly contrasting findings. This hypothesis should further be tested, with broader ranges of effort, as for example situations in which the tasks is unsolvable and the goal unreachable, to tackle the role of ACC in prompting engagement and disengagement.

Having unraveled the neural computations subserving reward and effort coding, the following question was how these signals influence actual behavioral policies. A first step in this direction was made in **Chapter 5**, by testing the hypothesis that reward and effort anticipation would influence the

motor system. To this end, we chose to use Transcranial Magnetic Stimulation (TMS), as a tool to stimulate the primary motor cortex (M1), in order to measure the excitability of the motor system via recording motor-evoked potentials (MEPs) on the hand muscles during task preparation. Previous research showed that motor excitability is influenced by a number of cognitive factors, including reward expectation (Gupta & Aron, 2011; Klein-Flügge & Bestmann, 2012). In this experiment, we manipulate both reward expectation and cognitive effort required by task. Both features are signaled by a cue prior to task onset. At this time, the TMS pulse on M1 is delivered. MEPs are recorded on the hand muscles, to test for a modulation of reward and effort. Strikingly, we show that both reward and cognitive effort anticipation modulate motor excitability in a non action specific way. This might reflect an increase in motor readiness to boost performance to achieve successful task completion. Interestingly, this effect is strongly modulated by individual differences in Need for Cognition, a trait measuring effort-related preferences and behaviors. This result is a promising first step in linking neural computation underlying value and effort with their behavioral consequences. Moreover, it shows that high level cognitive factors can exert a combined effect at the motor level. This opens exciting possibilities in investigating how more sophisticated computations can drive behavior, such as for example incorporating the effect of probability of success, and investigating how this is integrated with effort requirements and potential reward. Moreover, the potential effect of decision-making on the value-based modulation in M1 provides another interesting hypothesis to be investigated.

Finally, in the **General Discussion** we summarize the findings across the chapters, discussing implications for future research. Moreover, we

illustrate a new neuro-computational model of adaptive effort allocation, developed in parallel with our empirical research and partially derived from it. This model resolves the controversy between net-value and motivational accounts of cortico-limbic structures, by implementing motivation for effort as an adaptive behavior, which can be learned via reinforcement learning. The explanatory power of the model is illustrated, as well as its empirical predictions, yet to be tested. To conclude, the implications of our work for future research are discussed, as well as the potential relevance in clinical settings.

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CHAPTER 2
DISSOCIATING CONTRIBUTIONS OF ACC AND VMPFC IN REWARD PREDICTION, OUTCOME AND CHOICE [1]

Acting in an uncertain environment requires estimating the probability and the value of potential outcomes. These computations are typically ascribed to various parts of the medial prefrontal cortex (mPFC), but the functional architecture of this region remains debated. The anterior cingulate cortex (ACC) encodes reward prediction and outcome (i.e. win vs lose, Silvetti, Seurinck, & Verguts, 2012). An outcome-related value signal has also been reported in the ventromedial Prefrontal Cortex (vmPFC, Rangel & Hare, 2010). Whether a functional dissociation can be traced in these regions with respect to reward prediction and outcome has been suggested but not rigorously tested. Hence an fMRI study was designed to systematically examine the contribution of ACC and vmPFC to reward prediction and outcome. A striking dissociation was identified, with ACC coding for positive prediction errors and vmPFC responding to outcome, irrespective of probability. Moreover, ACC has been assigned a crucial role in the selection of intentional actions (decision-making) and computing the value associated to these actions (action-based value). Conversely, vmPFC seems to implement stimulus-based value processing (Rudebeck et al., 2008; Rushworth, Behrens, Rudebeck, & Walton, 2007). Therefore, a decision-making factor (choice vs. no choice condition) was also implemented in the present paradigm to distinguish stimulus-based versus action-based value coding in the mPFC during both decision and outcome phase. We found that vmPFC was more activated during the outcome phase in the no-choice than in the choice condition, potentially confirming the role of this area in stimulus-based (more than action-based) value processing.

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[1] Vassena E., Krebs R.M., Silvetti M., Fias W. & Verguts T. (2014). Dissociating contributions of ACC and vmPFC to reward prediction, outcome and choice. *Neuropsychologia*, *59*, 112-123.

INTRODUCTION

Humans constantly face Hamlet's dilemma in everyday life. Would you prefer a reliable job with a steady income over working on commission for high bonuses? Would you invest your savings in a pension fund or buy high-leveraged derivatives at the risk of a considerable loss? Adaptively choosing between an uncertain high profit versus a certain but smaller one involves predicting the probability of the profit, selecting one of the options, and verifying the outcome.

Foreseeing and detecting benefits are adaptive skills, essential in driving goal-directed behavior. In the human and in the non-human primate brain, these computations are mediated by the medial prefrontal cortex (mPFC, Haber & Knutson, 2010). The mPFC computes the expectation of an upcoming reward (i.e. reward prediction), as well as the violation of this expectation (Amiez, Joseph, & Procyk, 2006; Jessup, Busemeyer, & Brown, 2010; Knutson & Cooper, 2005; Matsumoto, Matsumoto, Abe, & Tanaka, 2007; Silvetti et al., 2012). This violation is often termed prediction error and it occurs when an outcome is better (positive prediction error, PPE) or worse than expected (negative prediction error, NPE) (Sutton & Barto, 1998). However, several other related functions have been ascribed to the mPFC besides reward prediction and prediction error, such as integrating reward with potential associated costs, driving decision making (selecting among different available options) and computing the value of possible outcomes (Nee, Kastner, & Brown, 2011; Rushworth & Behrens, 2008).

A major point in this debate concerns the functional architecture of the mPFC (Bush et al., 2002; Shackman et al., 2011). On the one hand, the anterior cingulate cortex (ACC) plays a critical role in reward prediction and prediction error coding (Jessup et al., 2010; Kennerley, Behrens, & Wallis, 2011; Silvetti et al., 2012). On the other hand, a complementary role in outcome coding has been hypothesized for ventromedial prefrontal cortex (vmPFC, Kennerley & Wallis, 2009; O'Doherty, Deichmann, Critchley, & Dolan, 2002; Rushworth, Noonan, Boorman, Walton, & Behrens, 2011), which seems to establish stimulus-outcome associations and encode rewarding features (i.e. value) of a stimulus (Bartra, Mcguire, & Kable, 2013; Chib, Rangel, Shimojo, & O'Doherty, 2009; Grabenhorst & Rolls, 2011; Sescousse, Caldú, Segura, & Dreher, 2013). This suggests a regional specialization within the mPFC with respect to reward prediction, prediction-error computation and outcome coding (Hare, Doherty, Camerer, Schultz, & Rangel, 2008). However, this hypothesis has not been directly tested in humans.

Another core aspect of decision making is action selection, and it also has been attributed to the mPFC (Brass & Haggard, 2007; Holroyd & Coles, 2008; Venkatraman & Huettel, 2012). Often this process is modulated by reward prediction, as selecting riskier options (low probability of reward) seems to be associated with increased mPFC involvement (see Platt & Huettel, 2008 for a review). However, how action selection is linked to reward prediction and outcome computation across different phases of the decision-making process still lacks a systematic account.

To tackle these issues, the present fMRI experiment manipulated reward prediction, outcome, and choice to systematically characterize the functional architecture within the mPFC. In a gambling task, participants were confronted with two options in each trial, namely a gamble and small sure win. The gamble

induced a reward prediction that would be sometimes violated, causing prediction errors. In half of the cases, participants could select the preferred option (choice condition) while in the other half, one option would be selected by the computer (no-choice condition).

A whole-brain analysis was performed to identify prediction-error- and value-related signals. A subsequent set of ROI analyses aimed at disentangling regional specificity of this signal throughout the mPFC across different conditions and different phases. Further analyses also elucidated the contribution of mPFC to action selection by comparing choice and no-choice conditions during both decision and outcome phase.

MATERIALS AND METHODS

Participants

Twenty-three healthy volunteers participated in this experiment (12 females). Two subjects were excluded from further analyses due to excessive head motion (more than 3 mm motion in either rotation or translation). One subject was excluded from further analysis due to poor task performance: This participant never selected the gamble options in the choice condition, thus failing to provide data for the prediction error conditions of interest (see Experimental Procedure section for a detailed description of the paradigm). The reported results are thus based on 20 participants with a mean age of 21.9 (range 20-26). The experimental protocol was approved by the Ethical Committee of the Ghent University Hospital. All participants signed an informed consent form before the experiment, and confirmed they had no neurological or psychiatric history.

Experimental Procedure

A gambling task was designed (Figure 1), adapting the paradigm used by Jessup et al. (2010).

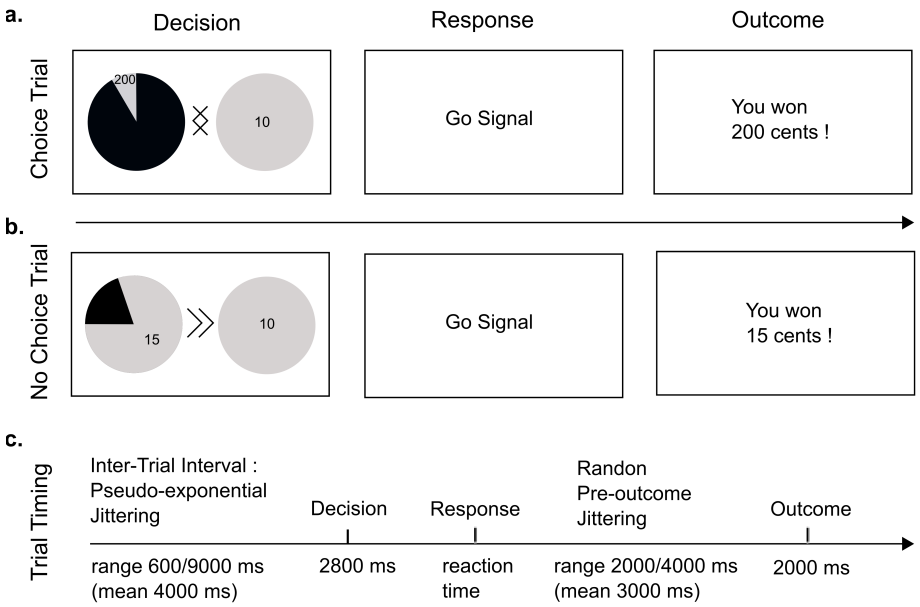

Figure 1: Task structure. During the decision phase, two options are presented on the screen. Each option represents the probability of winning (in grey; but in orange in the actual experiment) a certain amount of money (in cents, written in the grey slice). The complementary (in black; but in blue in the actual experiment) part of the pie is the probability of not winning on that trial. After 2800 ms, a go signal is presented, and the participant can choose one of the two pies. Subsequently the outcome is presented (win or lose). a. Example of a trial in the choice condition: when the central arrows are pointing in the opposite direction, the participant can freely decide which option to pick. In this example, the gamble option is risky (low probability of winning) with a high pay-off. Note though that the factor gamble type (low / high winning probability) was

systematically crossed with factor choice / no choice. b. Example of a trial in the no choice condition: the participant is forced to select the option indicated by the two arrows. In this example, the gamble option is safe (high probability of winning) with a low pay-off. c. Trial timing: the Inter-trial Interval is jittered in a pseudo-exponential fashion, ranging from 600 to 9000 ms (mean 4000). The duration of the decision phase is 2800 ms. As the go signal appears, the participant is allowed to respond. A randomly jittered interval precedes the outcome (range 2000/4000 ms, mean 3000 ms). The outcome presentation concludes the trial and its duration is 2000 ms.

At the start of every trial, two options were presented on the screen, namely a gamble and a sure win. Both options consisted of probability pies, where the grey slice indicated the probability of winning while the black slice showed the probability of not winning anything (defined from now on as losing for simplicity). Within the grey slice a number was presented, indicating the current amount of money at stake. One option was always the "sure win" pie, which was completely grey. The participants were informed that the size of the color pies indicated the probability of the events of winning or losing, without explicitly mentioning the exact probabilities. Thus the gamble pies were used to produce different prediction-error conditions.

Two types of gamble were presented: a risky gamble with a low probability of winning but a very high pay-off; and a safer gamble with a high probability of winning but a lower pay-off (Figure 1). Importantly, the expected value of the gamble (amount of money at stake multiplied by the probability) was in each case approximately equal to the sure win option. In order to introduce some variability to make the task more engaging, in the risky gamble the potential win varied between 110 and 114 cents with a 5% probability of winning. In the safer gamble it varied between 12 and 16 cents with a 80% probability of winning. As a consequence, winning a risky gamble would produce a positive prediction error (unexpected win) while losing a risky

gamble would represent a fulfilled prediction (expected loss). Conversely, winning a safe gamble would reflect an expected win while losing a safe gamble would evoke a negative prediction error (unexpected loss). The probability indicated by the safer gamble pie was always reliable. The probability indicated by the risky gamble pie was in fact slightly higher (shown probability 5%, actual probability 10%), in order to allow the participant to experience the positive prediction error situation in a sufficient number of trials. At the end of the experiment participants were asked if they found the probabilities shown by the pies reliable, which was the case for everyone.

On top of the prediction error manipulation, choice was introduced in the design as additional factor. In half of the trials, participants were given the possibility to select their preferred option (choice condition), while in the remaining trials one of the options would be randomly selected by the computer (no-choice condition, with half of no-choice trials giving the automatic selection of a gamble, and half of a sure win). In order to maximize visual similarities in the two conditions, a no-choice trial was signaled by two arrows presented between the pies pointing in the same direction, indicating the option to be selected, whereas in a choice trial two arrows pointing in opposite directions were displayed on top of each other (Figure 1). The presentation was randomized and the conditions were fully crossed (each gamble type appeared the same number of times in the choice and in the no-choice condition).

In order to keep the timing of the motor response as comparable as possible in both choice and no-choice condition, participants had to wait for a go-signal after the presentation of the pies. The response execution was followed by a randomly jittered interval (2 to 4 seconds, mean 3 seconds). Subsequently, the outcome was displayed, indicating the respective win or loss. The post-outcome inter-trial interval was also jittered (pseudo-exponential

distribution ranging from 600 milliseconds to 8 seconds, mean 4 seconds). The entire experiment consisted of 288 trials divided in three blocks, for a total duration of 60 minutes. The different trial types were randomly interleaved to be suitable for event-related analysis. During the break between blocks, the participants were asked via headphones to estimate how well they thought they were performing, in order to keep subjects focused on the task.

fMRI Data acquisition

Structural and functional images were acquired through a 3T Magnetom Trio MRI scanner (Siemens), using a 32-channel radio-frequency head coil. First, an anatomical T_1 weighted sequence was collected, resulting in 176 high-resolution slices (TR = 1550 ms, slice thickness = 0.9 mm, voxel size = 0.9 × 0.9 × 0.9 mm, FoV = 220 mm, flip angle = 9°). Subsequently, functional images were acquired using a T_2* weighted EPI sequence (30 slices per volume, TR = 2000 ms, slice thickness = 3mm, distance factor = 17%, voxel size = 3.5 × 3.5 × 3.0 mm, FoV = 224 mm, flip angle = 80°). On average 550 volumes per run were collected during 3 runs.

fMRI Data analysis

The first 4 volumes of the functional scans were discarded to allow for steady-state magnetization. The data were preprocessed with SPM8 (http://www.fil.ion.ucl.ac.uk/spm). Images were realigned to the first image of the run. The structural T_1 image was coregistered to the functional mean image to allow a more precise normalization. The unified segmentation and nonlinear warping approach of SPM8 was applied to normalize structural and functional images to the MNI template (Montreal Neurological Institute). Functional images were then smoothed with a Gaussian kernel of 8 mm full width half maximum (FWHM).

Subsequently a General Linear Model (GLM) was applied in order to identify each subject's condition-specific activation. Three factors were manipulated, namely probability of winning (low, high), outcome (lose, win), and choice (choice, no choice). This was applied to both decision phase and outcome phase. Hence, sixteen different conditions were modeled, crossing probability of winning (low / high), outcome (win / lose), choice (choice / no choice), and phase (decision / outcome). The factors probability of winning and outcome together define expected loss (low probability of winning+lose), positive prediction error (low probability of winning+win), negative prediction error (high probability of winning+lose), and expected win (high probability of winning+win).

Trials in which participants selected the sure win were modeled separately and were not considered for further analysis (as in Jessup et al. 2010). One regressor of no interest was added to model trials in which errors were made, namely when in the no-choice condition the response did not match the instructed response, thus excluding error-related activation from the analysis. Six subject-specific regressors were added modeling motion parameters obtained from the realignment. The resulting stimulus functions were convolved with the canonical hemodynamic response function. To account for low frequency noise a 128 s high pass filter was included. To account for serial auto-correlation, an autoregressive model was applied.

At the second level, we first concentrated on the *outcome phase*. A random-effects analysis was performed. A 2 × 2 × 2 factorial design was modeled, with choice (choice / no choice), outcome (lose / win) and probability of winning (low / high) as factors. All the reported whole-brain results where subjected to a voxel-level threshold of 0.001 uncorrected and survived a cluster-level family-wise error (FWE) correction for multiple comparisons with a p-

value of 0.05. First, the main contrasts were computed, namely main effect of choice, main effect of outcome, main effect of probability, and outcome by probability interaction (prediction-error-related activity, cf. Jessup et al. 2010). It should be noted that the focus was on the interaction contrast, in order to identify prediction-error signals. The contrast reflecting the main effect of probability is in fact not optimized in this design, as it might be confounded with reward magnitude. Furthermore, additional pairwise contrasts decomposing the interaction were computed.

Subsequently the main goal of the study was addressed, namely a precise identification of the respective contributions of ACC and vmPFC to the response to reward prediction, outcome and choice. These areas have often been reported to be implicated in one or more of these processes. Therefore, as strongly hypothesis-driven approach, two region-of-interest (ROI) analyses were performed. First a functional ROI approach was adopted, where two ROIs were defined on the basis of previous studies. Importantly this guarantees an unbiased selection with respect to the whole-brain significant prediction error and outcome signals. The ROI encompassing the vmPFC was defined on the basis of a meta-analysis performed on several imaging studies involving reward (Liu, Hairston, Schrier, & Fan, 2011). In that study, two clusters are reported in the medial Orbito-Frontal Cortex (mOFC, left and right) to be activated when receiving a positive outcome. As a note, the anatomical definition of mOFC and vmPFC in fMRI studies overlap (Rushworth et al., 2011). We centered the vmPFC ROI (20 × 10 × 10 mm) on the averaged coordinates from left and right mOFC from Liu et al. (2011), in order to encompass both left and right vmPFC (MNI coordinates x=0 y=51 z=-10), as no specific lateralization could be hypothesized from previous evidence. The ROI targeting the ACC was derived from the study of Nee et al. (2011), where a systematic analysis of mPFC was

carried out. The ACC ROI was not defined on the basis of Liu et al. because the factor probability was not included in that meta-analysis. Conversely, after identifying whole-brain effects, Nee et al. defined multiple ROIs from previous studies investigating different functions attributed to the ACC, among which conflict processing and error monitoring. One area was defined as anterior rostro-cingulate zone (aRCZ). This proved to be the area most sensitive to unexpected events. For this reason this seemed to be the most appropriate ROI selection, as we were targeting prediction-error coding. It should be noted that a recent meta-analysis focused on prediction error (Garrison, Erdeniz, & Done, 2013), but only studies involving model-based fMRI were included, thus making it not the most appropriate comparison for the current paradigm. Further research should focus on studies testing prediction error in decision-making paradigms (i.e. Jessup et al 2011) and perhaps perform ad-hoc meta-analysis (Wager, Lindquist, & Kaplan, 2007), thus granting an even more functionally precise ROI selection. To our knowledge, only a small number of studies addressed prediction-error under these conditions, thus making a meta-analysis currently unreliable. For these reasons the ROI from Nee et al. was selected. We centered our ACC ROI (also 20 × 10 × 10 mm) on the coordinates of the aRCZ-ROI (MNI coordinates x= 0 y=28 z=31). As for the vmPFC, no laterality hypothesis could be formulated and therefore the ROI covers symmetrically left and right ACC (as displayed in Figure 4a).

Second, an anatomical ROI approach was adopted, in order to provide convergent evidence for the previous analysis, to grant a more systematic and extensive sampling of the whole mPFC surface, and to ensure unbiased selection. Six box-shaped ROIs (10 mm wide) were anatomically defined sampling across the entire mPFC, starting from the posterior boundary of the Anterior Cingulate Cortex (ACC), as defined by the Brodmann area 24. The

ROIs were medially centered, in order to sample from both left and right mPFC. The subsequent selection of regions was determined by progressively shifting the ROI center along the rostro-caudal axis. In order to follow the anatomical architecture of the mPFC the center of the two more rostral ROIs was also shifted lower on the dorso-ventral axis to cover peri-genual ACC and ventromedial prefrontal cortex (vmPFC, see Figure 5a). As a result, 6 ROIs were obtained, 4 lying within the caudal to medial part of the ACC, one covering the peri-genual cingulate cortex, and one encompassing the vmPFC.

Condition-specific activation (percent signal change) was extracted from each ROI (both functional and anatomical) using the Marsbar Toolbox (Brett, Anton, Valabregue, & Poline, 2002) and submitted to a repeated-measures analyses of variance.

Subsequently, a separate second-level analysis was performed focusing on the *decision phase*, i.e., time-locked to the onsets of the display showing the pies. Specifically, a random-effects analysis was performed by implementing a 2 × 2 factorial design, with choice (choice/no choice) and probability of winning (low/high) as factors. The probability of winning could be 5% (low), leading to a risky gamble; or 80% (high), leading to a safe gamble. The voxel level threshold was set to 0.001 uncorrected and FWE cluster-level correction for multiple comparisons was applied, with a p-value of 0.05. Moreover, the same functional ROI procedure used for the outcome phase, was applied to the decision phase, to better characterize contributions of these areas to decision-making as well.

RESULTS

Behavioral results

Subjects chose the uncertain option over the sure win on 60% of the trials. On average, participants chose 47,05 (±15,82) of the risky gambles (67,14 % of the total) and 54 (± 21,78) of the safe gambles (72,97 % of the total, Figure 2a).

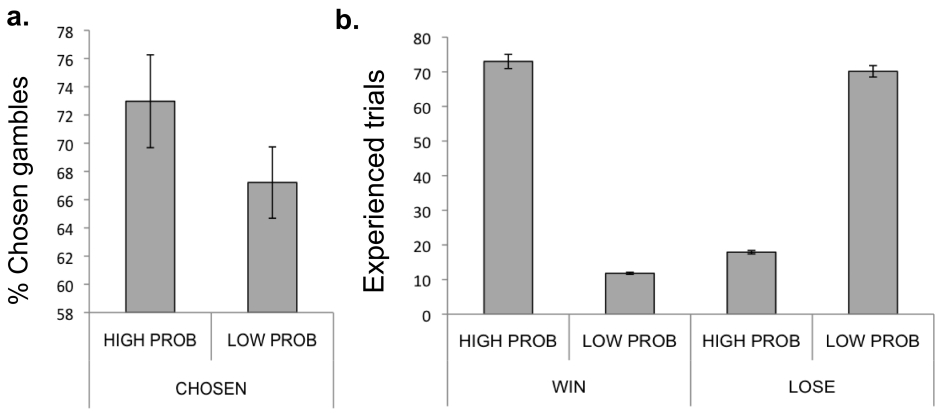

Figure 2: Behavioral results. a. Percentage of chosen gambles (over the sure win), for the high probability of winning gamble (HIGH PROB) and the low probability of winning gamble (LOW PROB). b. Average number of experienced trials per condition. In both plots, error bars denote 1 standard error of the mean.

The frequency of selection of the safe gamble over the sure win did not differ significantly from the frequency of selection of the risky gamble over the sure win ($t_{(19)}$ =.737, p=.47). As a result, participants experienced on average 11,8 (± 2,69) low probability + win trials, 17,9 (± 4,41) high probability + lose trials, 73 (±18.35) high probability + win trials, and 70,15 (±14,73) low probability + lose trials (Figure 2b).

Outcome-phase whole-brain fMRI results

The activation results during the outcome phase are reported in Table 1. The outcome contrast (win > lose) activated the vmPFC, ACC, striatum bilaterally, DLPFC bilaterally, brainstem, Posterior Cingulate Cortex (PCC) (Figure 3a). In the reverse outcome contrast (lose > win), no clusters survived. The probability contrast (low probability > high probability) activated the ACC, pre-SMA, brainstem, striatum bilaterally and insula bilaterally. The activation in this contrast is, however, difficult to interpret as probability covaries with reward magnitude in the present design. The contrasts computed for the main effect of probability and the main effect of outcome elicited a widespread whole-brain level activation. This resulted in big clusters, potentially invalidating the regional validity of the cluster-level inference (Woo, Krishnan, & Wager, 2014). For this reason, the voxel-wise FWE (p=.05) corrected results are also reported (see Table 1).

The whole-brain prediction error contrast (whole-brain interaction outcome by probability) yielded a consistent activation in the ACC, bilateral insula, bilateral striatum, brainstem and pre-SMA (Figure 3b). This pattern consistently reflects activity elicited by unexpected outcomes in previous studies (Jessup et al., 2010; Nee et al., 2011; Silvetti et al., 2012).

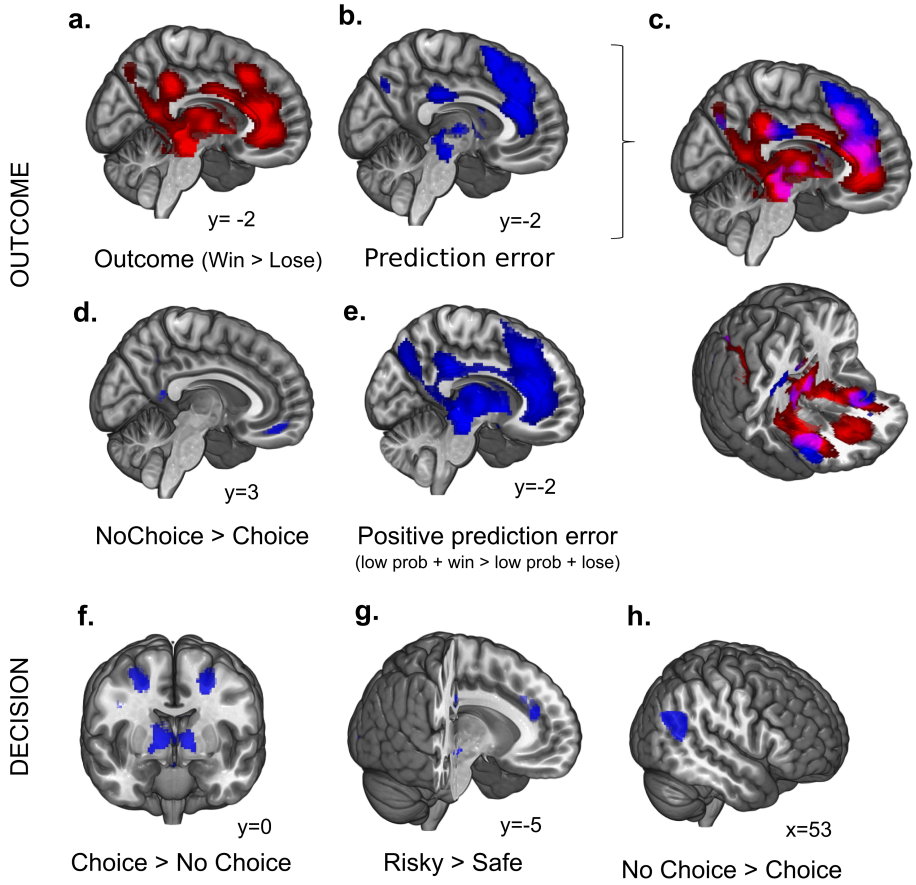

Figure 3: Whole brain contrasts

Outcome phase: a. Outcome contrast (Win > Lose). b. Prediction error contrast (outcome by probability interaction). c. Outcome contrast (in red) and prediction error contrast showing partial overlap, as well as selectivity for outcome in the vmPFC and prediction error in ACC. d. No Choice>Choice contrast. e. Positive prediction error contrast (low probability + win>low probability + lose).

Decision Phase: f. Choice>No Choice contrast. g. Risky gambles >safe gambles contras. h. No Choice>Choice contrast.

In a next step, in order to explore differences and commonalities in outcome and reward prediction coding, the prediction error contrast (outcome by probability interaction) and the outcome contrast (win>lose) were plotted together in Figure 3c. This showed partial overlap (displayed in violet) of outcome (in red) and prediction error (in blue). From this plot one can detect a first indication of selectivity for outcome versus prediction error coding along the mPFC; however, this claim remains exploratory at the whole-brain level. In the following section, the targeted ROI analyses will be discussed, providing a systematic and statistically sound investigation of different contributions of vmPFC and ACC.

Furthermore, the pairwise contrasts decomposing the interaction were computed (low probability + win > high probability + win, high probability + lose > low probability +lose). These contrasts revealed that the interaction pattern was mainly driven by the response to low probability + win outcomes (Figure 3e), as further clarified by the ROI analysis (see below). This seems to highlight a power problem to detect prediction error related activity in the high probability + lose outcomes. Jessup et al. (2010), from which our paradigm was adapted, found such a pattern for the analogous contrast in the Insula and the ACC. The reasons for these discrepancies should be investigated in further research.

Finally, a main effect of choice condition was reported. In particular a stronger response in the no-choice condition was observed in the vmPFC (Figure 3d) and in the left temporo-parietal junction (TPJ). Note that the main effect in the vmPFC was driven by a difference in deactivation (Figure 4e), as it is commonly found in this region (Raichle et al., 2001). As further noted by Rushworth et al. (2011, p.1057), “activations reported in vmPFC actually correspond to different degrees of deactivation”.

Table 1: Summary of the activation results

Area	*MNI Coordinates x y z*	*cluster level FWE*	*cluster level FDR*	*cluster size*	*peak T*
Outcome Phase					
Outcome (Win > Lose)					
Left pallidum	-12 6 -2	0.000	0.000	43399	9.42
Right pallidum	12 10 -2				8.79
Putamen	18 4 -8				8.43
Inferior temporal gyrus	-52 -54 10	0.001	0.001	541	7.43
Occipital cortex	-18 -96 -2	0.002	0.001	507	5.62
Outcome (Win>Lose) voxel-wise FWE					
Left pallidum	-12 6 -2	0.000	0.000	5052	9.42
Right pallidum	12 10 -2				8.79
Putamen	18 4 -8				8.43
Left inferior frontal operculum	-44 6 26	0.000	0.000	1712	7.98
Inferior frontal gyrus	-38 34 10				6.82
	-46 44 14				6.64
Anterior cingulate cortex	-6 34 6	0.000	0.000	3355	7.76
	8 28 14				7.67
	0 38 -2				7.53
Right inferior frontal operculum	44 10 26	0.000	0.000	1123	7.55
Right inferior frontal gyrus	44 36 16				6.18
Inferior temporal gyrus	-52-54-10	0.000	0.000	186	7.43
Occipital cortex	28 -92 -4	0.000	0.000	527	7.41
Inferior occipital gyrus	40 -82 -10				6.88
Right inferior temporal gyrus	56 -52 -12	0.000	0.000	289	7.22
Poster cingulate gyrus	8 -36 32	0.000	0.000	472	7.14
Angular gyrus	32 -58 42	0.000	0.000	1185	6.84
Right precuneus	36 -70 34				6.57
Right inferior parietal lobule	46 -36 48				5.97
Left inferior parietal lobule	-50 -38 44	0.000	0.000	1347	6.55
Supramarginal gyrus	-42 -44 38				6.06
Precuneus	8 -56 18	0.000	0.000	277	5.29
	-8 -50 14				5.09
Mid-cingulate gyrus	-6 -6 32	0.000	0.000	242	6.23
	6 0 30				6.02

	6 10 26				5.62
Superior frontal gyrus	-26 22 56	0.000	0.000	398	6.2
Middle frontal gyrus	-26 12 62				5.94
	-28 34 48				5.54
Hippocampus	32 -10 -10	0.004	0.095	25	5.69
Occipital cortex	-18 -96 -2	0.000	0.002	100	5.62
Probability (Low probability > High Probability)					
Right insula	30 24 -6	0.000	0.000	23705	9.35
Left insula	-28 18 -4				8.83
Anterior cingulate cortex	8 36 14				8.03
Inferior parietal lobule	-30 -50 44	0.000	0.000	4684	5.63
Precuneus	30 -60 30				5.46
Supramarginal gyrus	46 -44 30				5.23
Inferior temporal cortex	-44 -58 -10	0.001	0.001	534	5.2
Fusiform gyrus	-36 -64 -8				4.78
Left occipital cortex	-18 -98 -6	0.025	0.015	274	3.99
Right occipital cortex	30 -88 2	0.035	0.016	250	3.93
Probability (Low probability > High Probability) voxel-wise FWE					
Right insula	30 24 -6	0.000	0.000	4756	9.35
Left insula	-28 18 -4				8.83
Thalamus	8 -8 2				7.37
Anterior cingulate cortex	8 36 14	0.000	0.000	2270	8.03
	-6 34 14				7.09
	6 32 24				6.69
Middle frontal gyrus	48 10 50	0.000	0.000	262	6.8
Righ precentral gyrus	48 10 34				5.53
Posterior cingulate cortex	-4 -28 28	0.000	0.000	384	6.62
Middle frontal gyrus	28 56 0	0.000	0.022	60	5.68
Inferior parietal lobule	-30 -50 44	0.000	0.001	150	5.63
Superior frontal gyrus	22 48 34	0.003	0.101	31	5.46
Precuneus	32 -70 30	0.000	0.000	164	5.46
Angular Gyrus	30 -56 44				5.08
Left precentral gurys	-46 2 54	0.013	0.340	10	5.25
Supramarginal gyrus	46 -44 30	0.004	0.126	26	5.23
Inferior temporal cortex	-44 -58 -10	0.004	0.132	24	5.2
Inferior frontal operculum	34 20 30	0.000	0.022	60	5.12
Inferior frontal gyrus	46 26 28				5.07

Prediction-error (Outcome by Probability interaction)					
Left insula	-32 22 -2	0.000	0.000	2653	8.04
	-32 14 -12				6.43
Inferior frontal operculum	-40 10 30				4.81
Right insula	32 24 -4	0.000	0.000	3845	7.79
Inferior frontal gyrus	46 20 6				5.86
Middle frontal gyrus	50 12 48				5.15
Anterior cingulate cortex	6 38 36	0.000	0.000	4453	5.87
	6 30 18				5.85
	6 30 38				5.69
Thalamus	10 -10 2	0.000	0.000	1803	5.46
Pallidum	-10 4 2				5.26
Midbrain	0 -20 -14				5.25
Posterior cingulate cortex	-6 -26 30	0.001	0.000	564	5.27
	6 -26 30				4.84
Left inferior parietal lobule	-32 -58 46	0.000	0.000	712	5.09
Angular gyrus	36 -56 42	0.000	0.000	846	4.95
	50 -60 46				4.32
Right inferior parietal lobule	54 -48 52				3.6
Righ precuneus	12 -68 36	0.005	0.002	401	4.9
Left precuneus	-8 -68 34				3.58
Middle temporal gyrus	56 -26 -10	0.016	0.005	310	4.38
	66 -40 -4				4.33
Angular gurys	56 -50 26	0.019	0.006	298	4.34
Left inferior parietal lobule	-48 -38 44	0.121	0.035	164	4.11
Positive prediction error (Low probability+win>high probability +win)					
Left insula	-30 20 -4	0.000	0.000	35265	9.12
Right insula	32 22 -4				8.99
Midbrain	6 -24 -14				8.52
Right inferior temporal gyrus	56 -52 -12	0.001	0.000	567	6.60
Middle temporal gyrus	64 -44 -2				4.63
	58 -40 -10				4.47
Left inferior temporal gyrus	-52 -54 -10	0.003	0.001	429	6.21
Occipital cortex	26 -94 -4	0.001	0.000	570	5.61
Positive prediction error (Low probability+win>high probabilit+win) voxel-wise FWE					
Left insula	-30 20 -4	0.000	0.000	2094	9.12
Right inferior frontal operculum	-40 10 28				8.23

Right insula	32 22 -4	0.000	0.000	5214	8.99
Midbrain	6 -24 -14				8.52
Left inferior frontal operculum	44 12 26				8.13
Anterior cingualte cortex	8 36 14	0.000	0.000	3363	7.90
	-4 38 6				7.81
Left inferior parietal lobule	-30 -56 42	0.000	0.000	1263	7.49
Angular gyrus	36 -58 42	0.000	0.000	777	7.41
Right inferior parietal lobule	48 -40 48				5.61
Posterior cingulate cortex	6 -34 32	0.000	0.000	723	7.22
No Choice >Choice					
vmPFC	-6 52 -14	0.044	0.030	234	4.18
Left superior temporal gyrus	-48 -2 -14	0.019	0.030	295	4.82
Right middle temporal gyrus	64 -10 -8	0.001	0.002	576	4.38
Right precentral gyrus	48 -18 60	0.036	0.030	249	4.16
Left TPJ	-42 -74 32	0.027	0.030	271	3.94
Decision Phase					
Choice > No Choice					
Left and right ACC	8 26 32	0.000	0.000	6291	6.86
Right superior parietal	28 -62 38	0.000	0.000	2508	6.85
Right insula	30 26 4	0.000	0.000	582	5.60
Left Superior parietal lobule	-24 -66 44	0.000	0.000	801	5.46
Left frontal superior gyrus	-24 -2 46	0.003	0.002	338	5.25
Left Insula	-24 20 6	0.000	0.000	685	5.20
Right middle frontal gyrus	44 36 20	0.012	0.006	259	4.49
Right inferior frontal gyrus	48 8 26	0.045	0.019	185	4.33
No Choice > Choice					
Left TPJ	-44 -60 16	0.000	0.000	1894	5.94
Right TPJ	62 -54 26	0.000	0.000	919	5.20
Left/Right precuneus	-4 -56 32	0.000	0.000	478	4.22
Risky Gambles > Safe Gambles					
Bilateral ACC	-10 36 20	0.018	0.021	235	4.17
Right middle occipital gyrus	30 -92 -2	0.001	0.002	424	6.07
Left middle occipital gyrus	-28 -92 -8	0.074	0.043	158	5.03
Left insula	-28 -20 -4	0.079	0.043	155	4.32
Right fusiform gyrus	40 -60 -12	0.090	0.043	148	3.88

Outcome-phase functional ROI analysis

The planned ROI analysis was performed on the outcome-phase prediction-error signal. The goal of this approach was to better characterize the whole-brain results, targeting ACC and vmPFC function in reward prediction, outcome and choice coding. This analysis was guided by the a-priori hypothesis formulated on the basis of previous evidence, that ACC would encode reward prediction and prediction error, while the vmPFC would encode the outcome (Jessup et al. 2010, Rushworth et al. 2011). With this approach, we were able to contrast directly vmPFC and ACC activity by testing the specific hypothesis of a functional segregation within the mPFC for prediction error vs. outcome coding. The percent signal change scores showed a clear contribution of the ACC to the prediction-error signal (Figure 4), where the strongest response was elicited by the positive unexpected outcome (Figure 4d). This was confirmed by a significant outcome by probability interaction ($F_{(1,19)}$=15.07. p=.001), irrespective of choice (no three-way interaction choice by outcome by probability, $F_{(1,19)}$=.79. p=.39). A main effect of outcome ($F_{(1,19)}$=37.96. p<.001) and a main effect of probability ($F_{(1,19)}$=67.76. p<.001) were also identified in the ACC, but these did not interact with choice either (interaction choice by outcome $F_{(1,19)}$=.08. p=.79, interaction choice by probability $F_{(1,19)}$=3.13. p=.10). The ACC thus showed the expected prediction error response (Figure 4d), but this was mainly driven by a positive prediction error signal (low probability+win > high probability win in the choice condition $t_{(19)}$=4.4, p<.001, and in the no-choice condition $t_{(19)}$=5.03, p<.001; high probability+lose >low probability + lose $t_{(19)}$= -1.59, p=.13 in the choice condition and $t_{(19)}$= 1.29, p=.21 in the no choice condition; cf. Jessup et al. 2010).

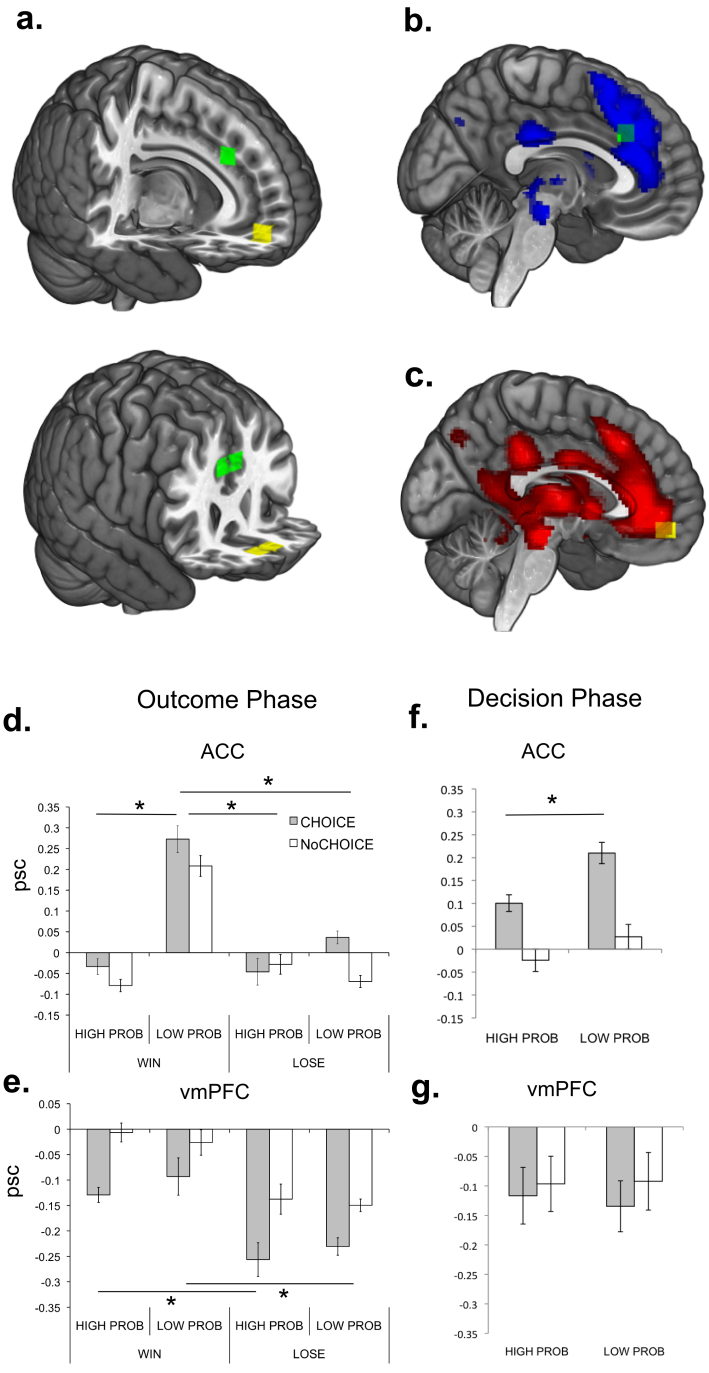
a.
b.
c.
d.
Outcome Phase
ACC
CHOICE
NoCHOICE
psc
HIGH PROB
LOW PROB
HIGH PROB
LOW PROB
WIN
LOSE
e.
vmPFC
psc
HIGH PROB
LOW PROB
HIGH PROB
LOW PROB
WIN
LOSE
f.
Decision Phase
ACC
HIGH PROB
LOW PROB
g.
vmPFC
HIGH PROB
LOW PROB

Figure 4: Functional ROI results

a. Region of Interest selection across the mPFC, guided by previous evidence (ACC in green, from Nee et al. 2011, vmPFC in yellow, from Liu et al. 2010). b. ACC ROI plotted on the whole-brain prediction error contrast (outcome by probability). c. vmPFC ROI plotted on the whole-brain outcome contrast (win > lose). d. Percent signal change analysis in the ACC during the outcome phase: choice-condition is reported in grey, no-choice condition in white. On the x-axis, the other two conditions are displayed, namely outcome (WIN/LOSE) and probability of winning (HIGH PROB/LOW PROB). On the y-axis, the percent signal change (psc) is represented. e. Percent signal change analysis in the vmPFC during the outcome phase: the choice condition is displayed in grey, the no-choice condition in white. On the x-axis, the other two conditions are displayed, namely outcome (WIN/LOSE) and probability of winning (HIGH PROB/LOW PROB). On the y-axis, the percent signal change (psc) is represented. f. Percent signal change analysis in the ACC during the decision phase. g. Percent signal change analysis in the vmPFC during the decision phase. In the plots error bars denote 1 standard error of the mean.

As hypothesized, the vmPFC selectively responded to positive outcome, irrespective of winning probability, thus showing no sensitivity to prediction errors (Figure 4e). Indeed, there was a main effect of outcome in this region ($F_{(1,19)}$=16.79, p=.001) and no significant outcome by probability interaction ($F_{(1,19)}$= .001, p=.98). Interestingly the vmPFC also showed a main effect of choice ($F_{(1,19)}$=13.7. p=.002).

The differential sensitivity of vmPFC and ACC was confirmed by a significant three-way interaction (region by outcome by probability) when vmPFC and ACC were both included in the analysis as additional “region” factor ($F_{(1,19)}$ =27.634 p<.001). Consistently, this analysis also reported a main effect of region ($F_{(1,19)}$=43.02. p<.001), an interaction region by choice

($F_{(1,19)}$=36.43. p<.001) and an interaction region by probability ($F_{(1,19)}$=17.23. p=.001).

Outcome-phase anatomically-guided ROI analysis

The anatomically-guided ROI analysis was performed on the outcome phase prediction-error signal. The percent signal change scores showed a contribution of the ACC to the prediction-error signal (Figure 5), where the strongest response was elicited by the positive unexpected outcome. Along the rostro-caudal axis, the rostro-medial portion of the ACC seemed to be the most sensitive to prediction errors, especially to the positive unexpected outcome (Figure 5b). A significant interaction between outcome and probability was detected in the medial ACC (ROI 2, $F_{(1,19)}$=6.66, p=.018), in the rostro-medial ACC ($F_{(1,19)}$=12.964, p=.002) and in the rostral ACC ($F_{(1,19)}$=13.910, p=.001), irrespective of choice. These regions showed the strongest prediction error response, as one can see in Figure 5c, where the prediction error size (as computed on the percent signal scores) is plotted as a function of anatomical location from caudal to rostral. This differential sensitivity within the ACC was confirmed by a significant three-way interaction between region, outcome and probability across the different ROIs within the ACC ($F_{(4,16)}$=7.597, p=.001). None of the regions showed a three-way interaction.

Strikingly, the vmPFC showed no sensitivity to prediction errors, but selectively responded to positive outcome instead, irrespective of winning probability (Figure 5b). Indeed, there was a main effect of outcome in this region ($F_{(1,19)}$=15.049, p=.001) and no significant outcome by probability interaction ($F_{(1,19)}$= .131, p=.721).

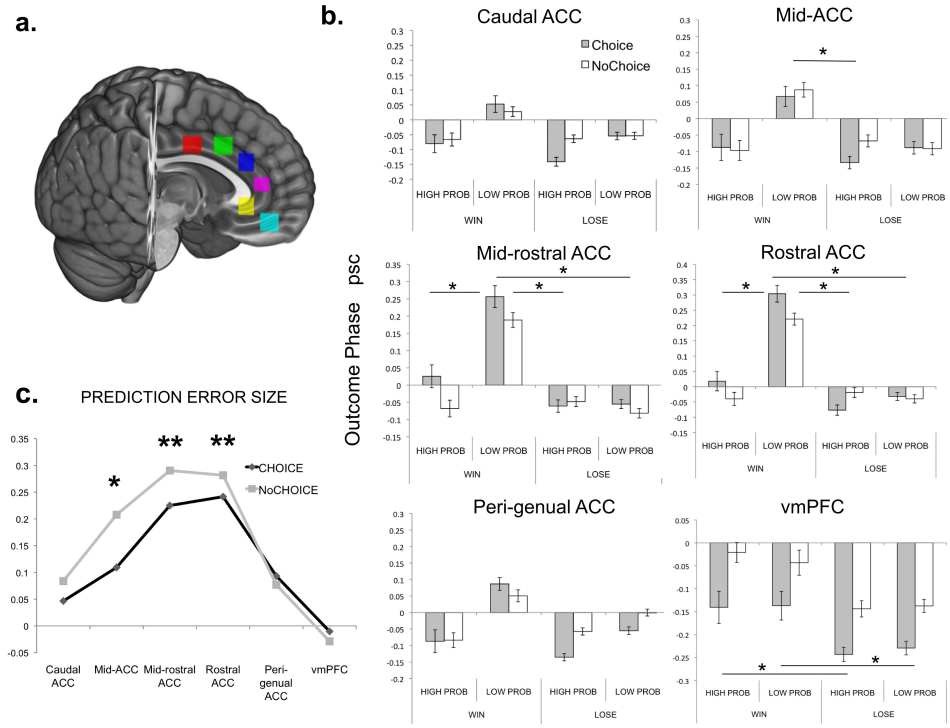

Figure 5: Anatomical ROI analysis

a. Anatomically-guided Region of Interest selection across the mPFC during outcome. b. Percent signal change analysis in the six ROIs (from caudal to rostral) during the outcome phase: choice condition is reported in black, no-choice condition in grey. On x-axes the four prediction error conditions are listed: Expected Loss, Positive Prediction Error (PPE), Negative Prediction Error (NPE), Expected Win. On the y-axes the signal change is represented. c. Prediction error size: intensity of the prediction-error-related activation in the six ROIs, from caudal to rostral, during the outcome phase. The intensity corresponds to the interaction size computed on the percent signal change scores ((low probability + win – low probability + lose) – (high probability + lose - high probability + win)). In black the choice condition is reported and in grey the no choice condition is reported. The intensity is maximal in the mid-ACC, mid-rostral ACC and rostral ACC.

Decision-phase whole-brain results

The results of the decision-phase analysis are summarized in Table 1. A main effect of choice was detected in the striatum (Figure 3f) and ACC, with a stronger response in the choice condition, confirming the role of these regions in action selection (Brass & Haggard, 2007; Holroyd & Coles, 2008). Increased activation in the left and right TPJ was observed in the no choice condition (Figure 3h).

A main effect of gamble type was also identified in the ACC (Figure 3g), in that it was more strongly activated when participants chose the risky (i.e., low winning probability) gamble as compared to the safe gamble (high winning probability), suggesting a contribution to risk estimation as well as risk-taking behavior.

Decision-phase functional ROI analysis

An additional ROI analysis of the decision phase was performed, based on the two functionally defined ROIs used in the outcome phase. It should be noted that in this analysis the trials where the sure thing was selected were not included (as in the outcome ROI analysis). ACC showed increased activity (in terms of percent signal change) for the low probability condition as compared to the high probability condition (main effect of probability, $F_{(1,19)=}15.38$, p=.001, see Figure 4f). Moreover, ACC showed a main effect of choice versus no choice ($F_{(1,19)}=42.54$, p<.001) but no interaction ($F_{(1,19)}=1.15$, p=.297). This corroborates the whole brain effect during the same phase. This activation might reflect ACC contribution in undertaking risky behaviors, as it is associated in this case with choosing (voluntarily or imposed by the computer) the risky option (over the sure win). In this case it is not possible to draw conclusions regarding reward prediction, as in this design the expected value was kept

constant, and this should be addressed in future research. No significant effect of choice or probability was reported in the vmPFC ROI (Figure 4g).

DISCUSSION

The current study investigated the functional architecture of the mPFC by targeting its contribution to reward prediction, outcome coding, and decision-making during a gambling task. A striking dissociation emerged between the ACC, being involved in reward prediction and (positive) prediction-error response, and the vmPFC, selectively coding for positive outcomes irrespective of probability. These findings support the hypothesis of a functional dissociation between ACC and vmPFC in prediction error and outcome coding. This idea received convergent indications from previous research but was to date not directly verified. We now discuss these and other results in the light of the current literature.

The pivotal role of mPFC in implementing and monitoring higher-order cognitive processes has been widely documented. A striking variety of different functions has been attributed to this area, ranging from reward prediction (Amiez et al., 2006; Silvetti et al., 2012), outcome coding (Rangel & Hare, 2010), reinforcement learning (Alexander & Brown, 2011; Silvetti, Seurinck, & Verguts, 2011), conflict monitoring and cognitive control (Blais & Bunge, 2010; Botvinick, Cohen, & Carter, 2004; Egner, Etkin, Gale, & Hirsch, 2008; Nee et al., 2011), to emotional regulation (Etkin, Egner, & Kalisch, 2011), prompting effortful behavior (Holroyd & Yeung, 2012; Vassena et al., 2014), and processing aversive and painful stimuli (Rainville, 1997).

Despite a wealth of research, no unifying comprehensive account has been formulated yet. The present study encompasses some elements that are

traceable in most, if not all, of these different domains. Specifically, prediction errors, outcome coding, and choice are cardinal components of all goal-directed behavior, yet they have not been manipulated in the same experiment in a systematic fashion. Our design allowed investigating the role of subparts of mPFC in each of these processes, thereby contributing to a comprehensive understanding of mPFC function.

Prediction-error signals were observed in the ACC, confirming previous reports (Jessup et al., 2010; Silvetti et al., 2012), as well as in the midbrain, striatum, pre-motor supplementary area (pre-SMA), supplementary motor area (SMA) and insula (see Figure 3b). The percent signal change analysis in the ACC revealed a sharp selectivity towards positive prediction errors, which elicited the strongest response (see Figure 4d). In contrast to one previous finding, negative prediction errors did not induce significant activity increases (cf. Jessup et al. 2010). As a matter of fact, single cell recordings in monkeys highlighted a difference in the distribution of prediction-error responses in the ACC, with a significantly smaller number of neurons producing a negative prediction-error signal (Kennerley et al., 2011). Furthermore, slight differences in the experimental paradigm could account for different activation patterns in our study compared to the Jessup et al. report , as the reward amounts in the current experiment were overall higher (while still respecting the proportions between conditions, and keeping the expected value constant across different options; cf. Jessup et al. 2010). The absence of negative prediction error signal might also be due to a power problem. The reward magnitude associated with the positive prediction error condition was indeed higher then in the negative prediction error condition (as in the original design of Jessup et al. 2010). A possible influence of reward magnitude cannot be completely excluded, even though the pattern emerging across different analyses (whole brain, functional

ROIs, anatomical ROIs) seems to suggest a magnitude effect in the vmPFC rather than in the ACC. This issue should be addressed in further research.

ACC was involved in encoding reward prediction (see Figure 4d and Figure 5b). This region consistently overlaps with clusters most commonly reported in previous studies (cf. Jessup et al. 2010, Nee et al. 2011, Silvetti et al. 2012). Importantly, prediction error signals in the ACC during the outcome phase were independent of the origin of the event (i.e., the choice condition). Specifically, the selectivity for positive prediction errors persisted irrespective of whether the option was selected by the person or by the computer. This is consistent with the findings of Kool et al. (Kool, Getz, & Botvinick, 2013). In an investigation of the behavioral "illusion of control" phenomenon, these authors did not find any modulation of intentionally accepting an option on neural prediction-error activity.

In contrast, the vmPFC was insensitive to prediction errors. Instead, the vmPFC displayed an outcome coding pattern, responding more strongly to the positive outcomes, irrespective of the winning probability that was tied to the selected option (see Figure 4e and Figure 5b). The role of vmPFC in reward prediction, especially with respect to the outcome phase, had not been clarified yet. The vmPFC is indeed assigned a crucial function in computing outcome expectancies (Tom, Fox, Trepel, & Poldrack, 2007), which might rely on a reward prediction (or prediction error) computation. However, similar responses have been observed for obtained as well as omitted rewards in this region (Kennerley & Walton, 2011). Although it has been argued that no prediction-error signal is computed by this area, to date opposing results have also been reported (O'Doherty et al., 2002; Schoenbaum, Roesch, Stalnaker, & Takahashi, 2009; Sul, Kim, Huh, Lee, & Jung, 2010).

However, vmPFC contributions in outcome coding have been widely documented (Noonan, Kolling, Walton, & Rushworth, 2012; Rushworth, Kolling, Sallet, & Mars, 2012). Specifically, activity in the vmPFC has been shown to correlate with the subjective value attached to the stimulus by the agent (Hare, Camerer, & Rangel, 2009; Padoa-Schioppa & Assad, 2008; Plassmann, O'Doherty, & Rangel, 2007) and to reflect the value of a chosen option (Boorman, Rushworth, & Behrens, 2013; Grabenhorst & Rolls, 2011; Kennerley et al., 2011). Furthermore, this region has been hypothesized to be the merging locus of value coding, where rewarding attributes of stimuli would be encoded in a common currency (Levy & Glimcher, 2012). Accordingly, vmPFC activity seems sufficient to decode the combined value of multi-attribute objects (Kahnt, Grueschow, Speck, & Haynes, 2011) and has been reported for both monetary and primary rewards (Kim, Shimojo, & O'Doherty, 2011). The current finding is consistent with this notion, but for the first time clarifies its strong dissociation with ACC in humans. It shows that its computation is independent of whether the positive outcome was predicted or not, and of whether the option had been intentionally selected or randomly assigned. Besides providing systematic insights on differential ACC and vmPFC functions, these results bridge human functional to primate neurophysiological results (Kennerley et al. 2011).

Furthermore, a main effect of choice was observed in the vmPFC during the outcome phase. The vmPFC was more active for outcomes following actions instructed by the computer (no choice > choice), without interacting with the value coding. This focus on the stimulus (i.e., no choice) features in absence of intentional action (i.e., choice) is in line with what has been proposed as a specialized encoding for stimulus-based value coding, implemented in the vmPFC, as opposed to action-based value coding, processed

by the ACC (Camille, Tsuchida, & Fellows, 2011; Rudebeck et al., 2008; Rushworth et al., 2007). The increased action in the vmPFC in this condition across all outcome types might thus derive from the absence of action selection. The potential functional role of this activation might be attentional in nature, with the purpose of underlying that the currently obtained outcome was not a consequence of an intentional choice, and therefore should not influence subsequent strategies (i.e. subsequent intentional choice). Albeit interesting, this interpretation is speculative and should be further addressed in future research. A possible alternative explanation would consider this activity to be Default Mode Network (DMN, Raichle et al. 2001) related. This region is indeed known to be part of the DMN. Moreover one can assume that the No Choice condition is less engaging, and this would justify DMN involvement. However, DMN activity would not coherently explain the outcome-value effect (increased activation for positive outcome). We therefore consider this second option less likely.

Increased activity in the no-choice condition was also observed in the left TPJ. A TPJ contribution is typically detectable whenever an action is performed by an external agent, such as a computer, as compared to when it is internally generated (Spengler, von Cramon, & Brass, 2009; Sperduti, Delaveau, Fossati, & Nadel, 2011). This may correspond to the same distinction between stimulus-based versus action-based value coding; however this interpretation remains speculative and requires further investigation.

Concerning the decision phase, the involvement of the ACC is evidently increased in the choice condition, as compared to the random (i.e., no choice) assignment. This is in line with studies on intentional action, where the ACC is reported as being more active while deciding between two options as opposed to an externally-driven selection (Brass & Haggard, 2007; Demanet, De Baene,

Arrington, & Brass, 2013; Forstmann, Brass, Koch, & von Cramon, 2006; Mueller, Brass, Waszak, & Prinz, 2007). The striatum was also more active in the choice condition. This has been previously related to the affective value associated with the possibility of choosing. Leotti and Delgado (2011) reported increased activation in the ventral striatum, while participants were exposed to cues predicting a trial where they could choose. This could potentially explain striatal involvement in our study as well.

The ACC also showed a stronger activation during the decision phase when a risky gamble was selected (low winning probability, high pay-off) as compared to a safe gamble (high winning probability, low pay-off). In other words, a stronger ACC involvement was triggered when people decided to choose a risky gamble over a sure small win, as compared to choosing a safe gamble over the sure small win. This suggests a role for ACC in undertaking a risky behavior. Notwithstanding the speculative nature of this hypothesis, understanding the neural mechanism underlying intentional selection of risky situations (low probability of reward) might provide useful insight with respect to pathological conditions, such as pathological gambling.

Interestingly, the no-choice condition in the decision phase also elicited a bilateral activation in the TPJ, again consistent with agency studies (Farrer & Frith, 2002; Spengler et al., 2009). However, the TPJ activation was mostly unilateral (right) in these studies. This difference may be explained by the increased relevance of our stimuli due to the reward manipulation.

CONCLUSIONS

The current study systematically investigated mPFC function in encoding three crucial components characterizing goal-directed behavior, namely reward prediction, outcome evaluation, and choice. A striking functional dissociation was detected within the mPFC: While ACC activity reflected reward prediction by signaling positive prediction errors, irrespective of whether the outcome derived from an intentional choice or a randomly selected option, the vmPFC selectively responded to positive outcomes, irrespective of the probability they were linked to. Although this dissociation did not interact with choice condition, vmPFC also carried a neural signature distinguishing between randomly selected (no choice) and intentionally chosen (choice) options. These findings provide new evidence for how complementary but dissociable information that is necessary to drive optimal goal-directed behavior is processed by different subregions within the mPFC.

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APPENDIX I. NEURAL CORRELATES OF INDIVIDUAL DIFFERENCES IN RISKY DECISION-MAKING

In **Chapter 2**, the contribution of mPFC to reward prediction, outcome value and choice was investigated. For these purposes, the analysis mainly focused on the *outcome phase,* that is when reward prediction is compared with the actual outcome by the ACC, and whose value is then encoded by the vmPFC. Some insights were also provided by a whole-brain analysis and region of interest analysis of the *decision phase.* This last analysis showed how mPFC is implicated not only in decision-making, but potentially also in encoding reward probability of a chosen option, which in the *decision phase* might be interpreted as uncertainty or risk. In fact, decision-making under uncertainty received considerable attention in neuroscientific research, given its relevance in several daily life situations, as well as in deviant behaviors such as pathological gambling. ACC activity has been consistently associated to risk estimation, and especially to undertaking risky behaviors, such as selecting a risky option over a sure win (Christopoulos, Tobler, Bossaerts, Dolan, & Schultz, 2009; Fukunaga, Brown, & Bogg, 2012; Huettel, Song, & McCarthy, 2005).

The behavioral results revealed a considerable variability in decision-making behavior across participants (See Chapter 2, Behavioral Result section, p. 61). Therefore our data were suitable to address one further question, concerning the underlying mechanisms of risk-preference in the current task. A better understanding of neural mechanisms underlying individual differences in risk-related behavior could provide useful insights on possible causes of pathological conditions, where risk estimation and risk preference play a pivotal

role. In fact this issue has been investigated in several studies, with different approaches, including neuropsychological and neuroimaging studies, and behavioral and personality studies (Bell, 2009; Gowin, Mackey, & Paulus, 2013; Leeman & Potenza, 2012; Llewellyn, 2008; Spurrier & Blaszczynski, 2013; van Holst, van den Brink, Veltman, & Goudriaan, 2010).

When targeting the neural substrate of this variability, a potential candidate is the region of the anterior Insula (aInsula). This region is implicated in risk estimation (Bossaerts, 2010; Singer, Critchley, & Preuschoff, 2009). Preuschoff and colleagues reported in a number of studies that aInsula shows increased activation as a function of risk, defined by the authors as outcome variance. (Preuschoff, Quartz, & Bossaerts, 2008; Rudorf, Preuschoff, & Weber, 2012). Furthermore, according to these results, aInsula seems to encode not only the predicted risk, but also a prediction error response, signaling when the experienced risk deviates from the expected risk. Other studies suggest that aInsula encodes skewness instead (i.e. asymmetry in the predicted reward distribution, (Burke & Tobler, 2011; Symmonds, Wright, Bach, & Dolan, 2011). Recent evidence is also provided by studies investigating risk preference in substance abusers. These studies reported decreased activation of aInsula during risky decisions (Claus & Hutchison, 2012; Crowley et al., 2010). Importantly, it has also been hypothesized that aInsula mediates not only risk estimation, but also risk avoidance (Kable & Glimcher, 2009; Rudorf et al., 2012). Taken together, these results support a crucial role of the aInsula in risky decision making. Hence, aInsula might mediate individual differences in risk preference. However, this hypothesis has not been tested in healthy subjects. Our task involved making a series of choices between risky gambles and sure wins, thus providing suitable data to test this hypothesis. More precisely, the goal of this analysis was to investigate neural correlates of individual differences in risk preference, targeting neural activation associated with

choosing a gamble. In this context, risk is operationalized as probability of losing (not winning anything in this experiment).

For these reasons, a new analysis was performed on the data collected for Chapter 2, (for the methods used in the original analysis, see Chapter 2, methods section, p. 56).This new analysis focused on the *decision phase*. A new first level GLM was set up, modeling all trials, irrespective of whether the gamble or the sure win was chosen (in contrast to the GLM in Chapter 2, where only the gambles were modeled). This resulted in 8 regressors of interest crossing 3 factors, namely choice (choice / no choice), gambling (choosing the gamble / choosing the sure win), and probability (low probability gamble / high probability gamble). Outcomes were also modeled, as in the previous analysis, resulting in 8 outcome-related regressors. Additionally, one regressor was added to account for breaks and erroneous responses, and 6 regressors were added to account for motion. A random-effect analysis was then performed, with the goal of isolating activity associated with choosing a gamble (entailing risk) over a sure win. The whole-brain contrast for the main effect of gambling was then computed, with a voxel-level threshold of p=.001 uncorrected and a cluster-level family-wise error (FWE) correction for multiple comparisons of p=.05.

Next, a behavioral measure of risk-preference was computed, calculating how many times participants selected the gamble over the sure win. Subsequently, the main analysis targeting individual differences was performed. A whole-brain regression analysis was carried out, with the gambling contrast as a dependent variable, and risk preference as a covariate. To this contrast, a voxel-level threshold of p=.001 uncorrected was applied, with a cluster-level FWE correction for multiple comparisons of p=.05. Importantly, in the current experiment the expected value of the two options was kept equal, as the primary goal of the experiment was to target value coding and prediction error in the *outcome phase*. This implies that activity during the *decision phase* cannot be

associated with value encoding, as both options have the same expected value (reward magnitude x probability). As a consequence, it is possible to disentangle activity specifically associated with choosing a gamble, that is choosing to take a risk.

On average, participants gambled in 68.34 % of the cases. The inter-individual variability in choices was substantial (standard deviation of 21.07). However, three participants did not show any variance in their choice behavior (either they chose the gamble in every trial, or the sure win in every trial). The data from these participants were excluded from this analysis, as the first level GLM could not be fit, given that not all conditions were represented in the data. The whole-brain analysis targeting the main effect of gambling showed motor-related activity, but no activation in the aInsula. This might be due to a power problem, given the frequency of occurrence of gambles and sure win (see Chapter 2, Figure 2). The individual differences analysis however (gambling contrast with risk-preference as a covariate) yielded activation in the right aInsula. Interestingly, aInsula was the only reported activation cluster (Figure A1, cluster size 317 voxels, T= 6.46, cluster-level p-value=.001, MNI coordinates of the local maximum x= 34 y = 24 z = -6).

More specifically, this revealed a negative correlation, thus showing that activity in the aInsula differentiated better between choosing to gamble and choosing a sure win in participants with lower risk preference. For illustrative purposes, the average percent signal change (psc) in the aInsula functional cluster was computed using the MARSBAR Toolbox (Brett, Anton, Valabregue, & Poline, 2002). This is plotted in figure A2 as a function of risk-preference.

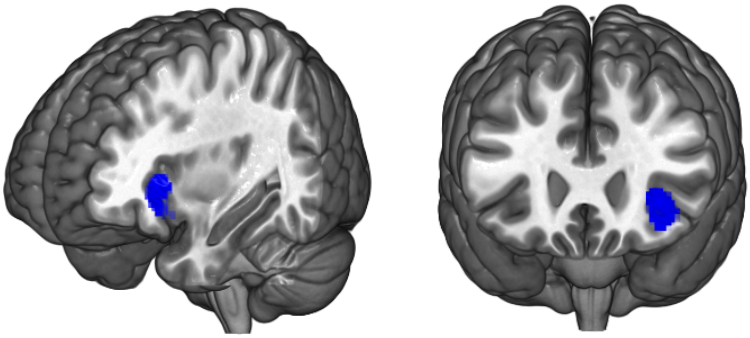

Figure A1: Whole-brain Gambling contrast, with risk-preference as a covariate. The sagittal and coronal view show an activation cluster in the right aInsula

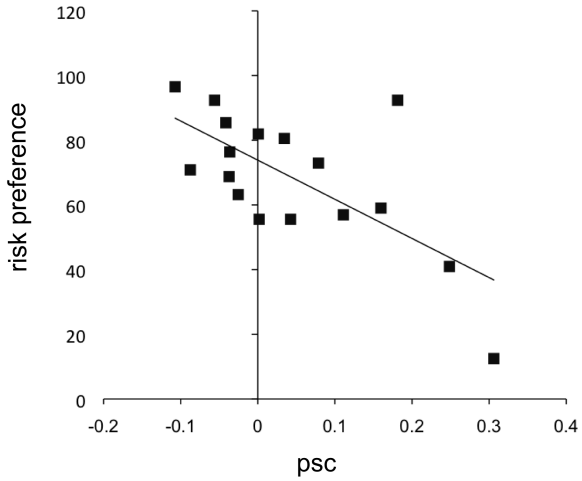

Figure A2: Percent signal change in aInsula in the Gambling contrast predicts actual gambling (risk-preference).

In the whole-brain analysis, the covariate predicts the difference between the two conditions composing the contrast, that is Choosing the gamble > Choosing the sure win. To better characterize this relationship, we checked if this effect was driven by choosing the gamble. The psc for the Choosing the gamble condition alone was indeed correlated to risk preference (r= -.62, p=.008). This was not the case for the Choosing the sure win psc (r=.34, p=.18). This result shows that increased aInsula activation when choosing a gamble was associated with lower risk-preference. In other words, people who gambled less, showed increased aInsula activation when gambling, while people who gambled more showed decreased aInsula activation when gambling. This result confirms a pivotal contribution of aInsula to risk-preference. In fact, this is in line with the results of one recent study, showing decreased aInsula activation in risk-seekers, even though in that study risk was quantified as outcome variance, and not as probability of losing (Rudorf et al., 2012). Further studies should keep this heterogeneity in the definitions of risk into account. One open question for instance is if the aInsula would similarly encode inter-individual variability in risk preference also when the alternative option would be a sure loss, instead of a sure win. As for the relevance of the current results, speculatively, decreased aInsula during gambling in people with higher risk preference might provide a potential etiopathogenetic mechanisms for the development of deviant behaviors. Choosing more often the risky option might be driven by an underestimation of the risk attached to this action. On the one hand, this altered risk estimation process might reflect a vulnerability, promoting risk-prone as opposed to risk-averse tendencies. On the other hand, hyper-activation of the same region might be associated with excessive behavioral inhibition. Given the potential relevance for clinical assessment and treatment of behavioral disorders, these hypotheses should be further investigated in future research.

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CHAPTER 3
OVERLAPPING NEURAL SYSTEMS REPRESENT COGNITIVE EFFORT AND REWARD ANTICIPATION [1]

Anticipating a potential benefit and how difficult it will be to obtain it are valuable skills in a constantly changing environment. In the human brain, the anticipation of reward is encoded by the Anterior Cingulate Cortex (ACC) and Striatum. Naturally, potential rewards have an incentive quality, resulting in a motivational effect improving performance. Recently it has been proposed that an upcoming task requiring effort induces a similar anticipation mechanism as reward, relying on the same cortico-limbic network. However, this overlapping anticipatory activity for reward and effort has only been investigated in a perceptual task. Whether this generalizes to high-level cognitive tasks, remains to be investigated. To this end, an fMRI experiment was designed to investigate anticipation of reward and effort in cognitive tasks. A mental arithmetic task was implemented, manipulating effort (difficulty), reward, and delay in reward delivery to control for temporal confounds. The goal was to test for the motivational effect induced by the expectation of bigger reward and higher effort. The results showed that the activation elicited by an upcoming difficult task overlapped with higher reward prospect in the ACC and in the striatum, thus highlighting a pivotal role of this circuit in sustaining motivated behavior.

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[1] Vassena E., Silvetti M., Boehler C.N., Achten E., Fias W. & Verguts T. (2014). Overlapping neural systems represent cognitive effort and reward anticipation. PLoS ONE, 9(3), e91008

INTRODUCTION

Reward processing has been investigated by several disciplines, ranging from economics to psychology and machine learning (Rangel, Camerer, & Montague, 2008). An established finding is that animals typically strive for the most beneficial consequences of their action, and that they do so via optimizing the net reward they can obtain from the environment (Kahneman & Tversky, 1979). This complex skill relies on reward estimation, which is precisely encoded in the primate and in the human brain (Alexander & Brown, 2011; Knutson & Cooper, 2005; Schultz & Dickinson, 2000; Silvetti, Seurinck, & Verguts, 2011, 2013). This consists in anticipating the value of the potential benefit. Nevertheless, benefits seldom come for free. They usually entail some cost, and this cost is taken into account by the brain to calculate the net value of each available option (Basten, Biele, Heekeren, & Fiebach, 2010; Kennerley, Dahmubed, Lara, & Wallis, 2009; Park, Kahnt, Rieskamp, & Heekeren, 2011; Walton, Rudebeck, Bannerman, & Rushworth, 2008). Usually, obtaining a benefit requires a certain degree of effort, either in terms of cognitive demand (Boksem & Tops, 2008) or physical energy expenditure (Kurniawan et al., 2010; Schweimer & Hauber, 2010; Walton, Kennerley, Bannerman, Phillips, & Rushworth, 2006). The more effortful the task, the less the animal values the respective reward (Assadi, Yücel, & Pantelis, 2009; Kurniawan, Guitart-Masip, & Dolan, 2011). Humans also discount reward by effort (Matthew M Botvinick, Huffstetler, & McGuire, 2009; Croxson, Walton, O'Reilly, Behrens, & Rushworth, 2009), meaning that subjective reward value decreases as a function of the effort required to obtain it. Hence, also effort needs to be estimated when calculating reward value, and a major role in this process has again been

attributed to the Anterior Cingulate Cortex (ACC) and the striatum. These structures would integrate predicted cost and reward in a net value signal (Basten et al., 2010; Walton et al., 2008).

Besides estimating reward and cost, expecting to earn a reward is a powerful motivational factor per se (Berridge, 2004). This can improve behavioral performance (Hübner & Schlösser, 2010) and influence learning and memory, according to a concept known as incentive-salience (Berridge, Robinson, & Aldridge, 2010; Berridge, 2004). At the neural level, the anticipation of a potential reward is associated with increased activation in the ACC and striatum (Knutson & Cooper, 2005).

Recent evidence suggests that facing an upcoming effortful task also induces increased ACC and striatum involvement. This might reflect a motivational effect towards task performance, comparable to the incentive given by a monetary reward (Boehler et al., 2011; Krebs, Boehler, Roberts, Song, & Woldorff, 2012; Stoppel et al., 2011). In terms of energy expenditure, this would be translated to the invigoration of the optimal behavior, which in turn is required to obtain a reward. Several findings in animals support this hypothesis, identifying its neural mediator in the fronto-striatal dopaminergic system (Salamone, Correa, Mingote, & Weber, 2005). Accordingly, if this circuit is pharmacologically inhibited (Bardgett, Depenbrock, Downs, Points, & Green, 2009) or lesioned (Walton et al., 2006) the ability of engaging in a high-demand task to obtain a reward is blunted. A recent fMRI study in humans (Kurniawan, Guitart-Masip, Dayan, & Dolan, 2013) also highlighted the contribution of this network in anticipating higher energy expenditure, in terms of a more effortful grip.

Thus, both reward and effort anticipation are core functions ascribed to ACC and striatum (Knutson & Cooper, 2005; Kurniawan et al., 2013; Silvetti et

al., 2013). How and whether these elements are combined when cognitive effort is required, recently received considerable attention (Matthew M Botvinick et al., 2009; Croxson et al., 2009; Hernandez Lallement et al., 2013; McGuire & Botvinick, 2010; Schmidt, Lebreton, Cléry-Melin, Daunizeau, & Pessiglione, 2012). However, findings concerning ACC and striatum are controversial. Krebs et al. (2012) made a first attempt towards clarifying this matter, by combining reward and effort in an attentional-cueing paradigm in order to probe for shared neural activation. In that study, both task demand (effort) and reward were manipulated in a perceptual task. The cue predicting the more effortful condition elicited a stronger activation of the midbrain and striatum, dopaminergic structures that broadly innervate the ACC (Haber & Knutson, 2010). Moreover, this nigro-striatal network partially overlapped with the activations elicited by the cue predictive of a high reward, and the ACC maximally responded to the high reward/high effort condition. These results are interpreted by the authors as part of a resource-recruitment process, essential in successfully accomplishing the task and hence obtaining the reward. Nevertheless, this result was obtained in a perceptual task where during the preparation period the allocation of attentional resources was crucial for successful completion. It is unclear if this finding extends to tasks requiring higher-level cognitive skills, thus relying on a more general preparation effect. This would argue in favor of a motivational effect, going beyond attentional-cueing facilitation. The contribution of the ACC in preparation for arithmetical tasks (Kong et al., 2005) and in logical-rules tasks (Sohn, Albert, Jung, Carter, & Anderson, 2007) would strongly suggest this mechanism to be a more general preparation effect, in line with theories of task-set preparation (Aarts, Roelofs, & van Turennout, 2008; Sterling, 2012), rather than a simple spatial-attention facilitation. However, this hypothesis has never been tested in demanding high-level cognitive tasks in combination with reward.

Hence, an fMRI experiment was designed where cognitive effort and reward prospect were manipulated in order to investigate effort and reward anticipation. The goal was to test for the cognitive equivalent of a behavioral invigoration signal, especially in the ACC and in the striatum.

Moreover, a third condition was added, where the delay in reward delivery was manipulated. Controlling the time variable is crucial, as effortful tasks typically require more time to be performed. Delay estimation is in fact a well-known mechanism both at the behavioral and the neural level (Green & Myerson, 2004; Kobayashi & Schultz, 2008; Peters & Büchel, 2011; Roesch, Taylor, & Schoenbaum, 2006) which in the light of the current purpose could be a potential confound. For these reasons the same task was implemented for both effort and delay conditions. Furthermore, this allowed to test the specificity of the motivational effect of the effort condition.

In the experiment, in each trial the cue phase informed about the upcoming reward, effort, or delay. The task consisted of solving arithmetic operations of different degrees of difficulty. In a first step, the anticipatory encoding of high-level cognitive effort and reward was tested, as well as their overlap (Krebs et al., 2012). This aimed at determining the type of encoding of these two variables. A motivational encoding would imply higher activation for higher effort and bigger reward, as those would serve as incentive to task performance. An alternative encoding would be value-related, where maximal response should be reported for the condition with the highest net-value (low effort and big reward). This putative shared substrate was also tested.

In a second step, selective response to the anticipation of cognitive effort was addressed in an exploratory analysis, to isolate a potential neural mechanism specifically supporting cognitive effort exertion, unrelated to reward.

MATERIALS & METHODS

Participants

Twenty-five healthy volunteers participated in this experiment (8 males). Three subjects were excluded from further analyses due to excessive head motion (more than 3 mm motion in either rotation or translation). This left 22 subjects (8 males), with a mean age of 20 (range 18-24). The experimental protocol was approved by the Ethical Committee of the Ghent University Hospital. All participants signed an informed-consent form before the experiment, and confirmed they had no neurological or psychiatric history.

Experimental procedure

An event-related fMRI design was set up, with the main manipulations being separated into different experimental blocks. In every block, reward, effort, or delay was manipulated, resulting in three different block types (Figure 1). Every block type was presented twice, resulting in six randomized blocks in the experiment. To avoid sequence effects, a block type was never preceded or followed by the same block type. Every block started with a display informing the participant about the block type (reward, effort, or delay block).

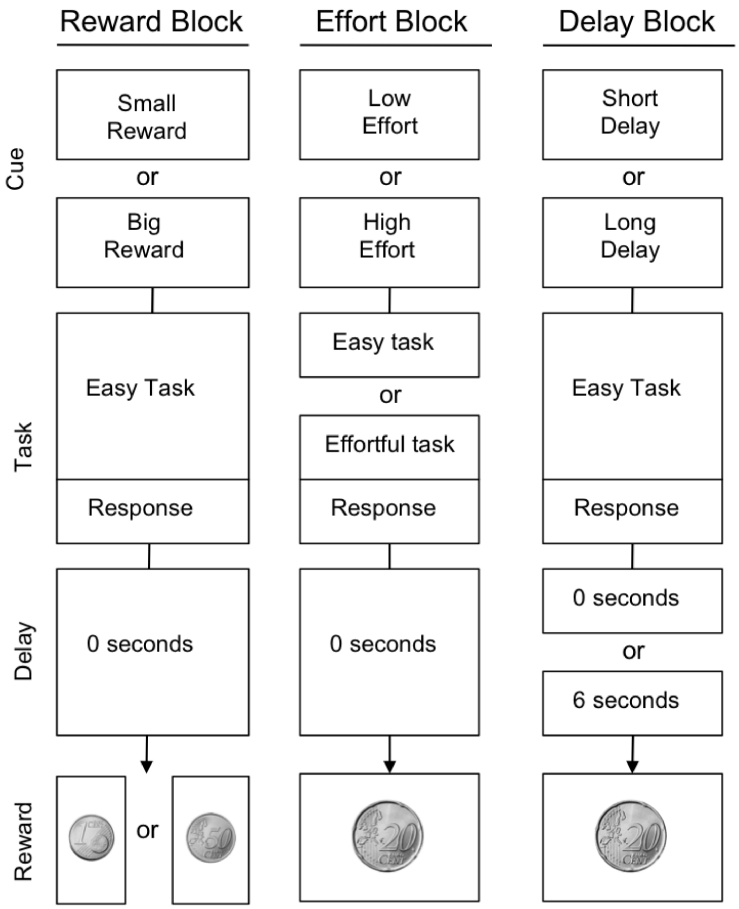

Figure 1: Task structure. Block types. In every block only one trial type is presented, where only one feature is manipulated. In a trial in the reward block, the cue informs about the final reward being small or big. In a trial in the effort block, the cue informs about the difficulty level (low or high). In the delay block, the cue informs about the length of the delay between response and reward delivery (short or long).

Every trial in a block started with a cue formed by two words, informing participants whether the manipulated feature (reward, effort, or delay) would be low or high (Figure 2).

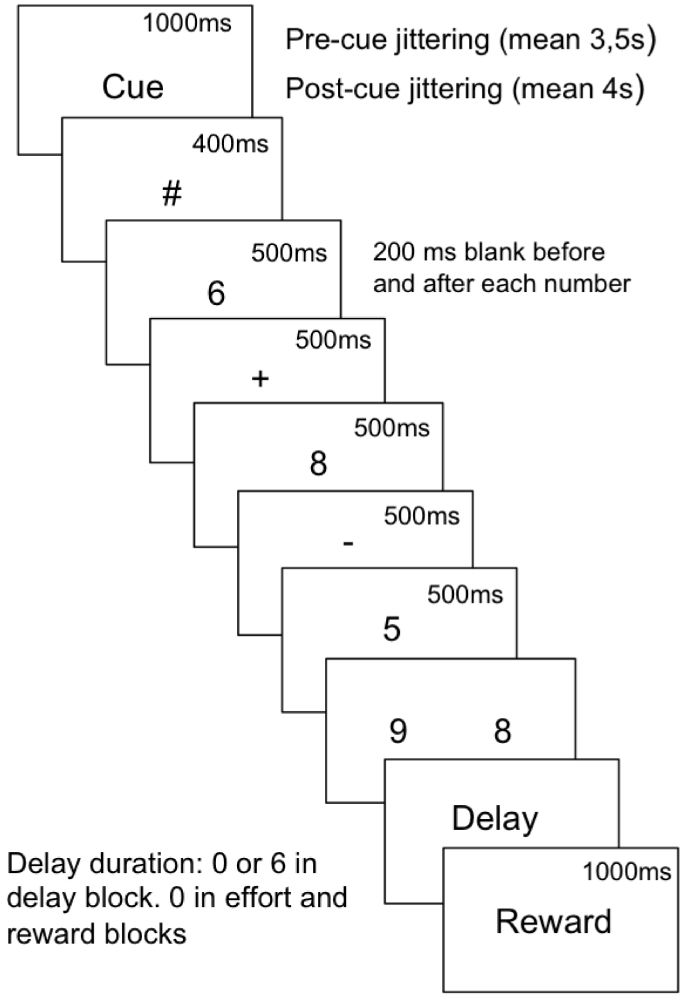

Figure 2: Task structure and timing. The cue presentation is followed by a fixation symbol. The task follows, consisting of an addition followed by a subtraction. Two possible results are presented and the subject has to choose the correct one. After the response, a delay can occur. If the response was accurate, the reward is shown.

The resulting six cues were “Small Reward”, “Big Reward”, “Low Effort”, “High Effort”, “Short Delay”, or “Long Delay”. Within a block, the presentation of different trial types (i.e. “Low Effort” and “High Effort”) was randomized. The inter trial interval (ITI) was randomly jittered (range 2-5 seconds, mean 3.5) as well as the period between cue onset and task onset (range 2-6 seconds, mean 4, Figure 2). At task onset, two subsequent arithmetic operations had to be performed, an addition followed by a subtraction. Participants had to mentally perform the calculation and then select the correct solution from two possible results by pressing the corresponding key (Figure 2). Correct responses were followed by positive feedback consisting of a picture of a coin representing the reward. Errors were followed by the word “incorrect”.

In the reward condition, the reward could be small or big, leading to a win of 1 cent or 50 cents after performing the easy version of the task, with no delay in reward delivery. In the effort condition, the task could be easy or difficult. In both cases it consisted in single digit calculations, but in the difficult condition every single operation required carrying or borrowing, whereas the easy condition did not (Imbo, De Rammelaere, & Vandierendonck, 2005). In this case the reward was constant at 20 cents, and there was no delay in delivery. In the delay condition, the interval between response selection and reward delivery could be short (no delay) or long (6 seconds). The task was easy and the reward constant at 20 cents. The cues were fully predictive of the manipulation, thus ruling out uncertainty confounds. Trials in the reward and effort blocks lasted on average 14 seconds, while trials in the delay block lasted on average 17 seconds. The experiment consisted of 180 trials in total (60 trials per condition, 30 trials per event), with each condition divided in two blocks. The participants underwent a short version of the experiment as training before the scanning session. They

were asked to be as fast and as accurate as possible. At the end of the experiment, they received the amount of money that they won by performing the calculations.

We focused our analyses on the cue period activity, thus avoiding potential confounds of actual effort, motor response activation, or differential delay. The experiment was implemented in E-prime 2.0 (www.pstnet.com/eprime; Psychology Software Tool) and presented to the participants using a dual display MRI compatible LCD display and mounted in a lightweight headset (VisuaStim XGA, Resonance Technology Inc., Northridge, CA; http://www.mrivideo.com/).

Ratings & questionnaires

Participants filled in a safety checklist prior to scanning and a post-scan checklist after the session. Every block was followed by a short break, in which the participant was asked to rate how much attention he had paid to the cues. These questions aimed at keeping the participant focused on the cue and avoiding potential distractions. At the end of the session participants filled in two more questionnaires. One questionnaire queried the pleasantness of each cue type and the pleasantness of the effective outcome related to each cue, in order to check whether the high cost options were perceived as less pleasant. The second questionnaire was the Bis/Bas (Carver & White, 1994), testing reward sensitivity, drive and fun-seeking tendencies.

fMRI data acquisition

Images were acquired through a 3T Magnetom Trio MRI scanner (Siemens), using an 8 channel radio frequency head coil. First, an anatomical T_1 weighted sequence was applied, collecting 176 high-resolution slices (TR = 1550 ms, slice thickness = 0.9 mm, voxel size = 0.9 ´ 0.9 ´ 0.9, FoV = 220 mm, flip angle = 9°). Subsequently, functional images were acquired using a T_2* weighted

EPI sequence (30 slices per volume, TR = 2000 ms, slice thickness = 3mm, distance factor = 17%, voxel size = 3.5 x 3.5 x 3.0, FoV = 224 mm, flip angle = 80°). The session was divided into 6 runs. On average 225 volumes per run were collected. Run length varied according to the block type, namely 7 minutes for reward blocks and effort blocks and 8.5 minutes for delay blocks.

fMRI data analysis

After discarding the first 4 volumes of each run to allow for steady-state magnetization, data were preprocessed with SPM8 (http://www.fil.ion.ucl.ac.uk/spm). Images were realigned to the first image of each run and the structural image was coregistered to the functional mean image to allow a more precise spatial normalization. The unified segmentation and nonlinear warping approach of SPM8 was applied to normalize structural and functional images to the MNI template (Montreal Neurological Institute). Functional images were then smoothed with a Gaussian kernel of 8 mm full width half maximum (FWHM).

Subsequently a General Linear Model (GLM) was applied in order to identify each subject's condition-specific activations. Cue onsets were modeled as events of interest (2 regressors per run) and two condition-specific task regressors (from stimulus onset to response, 2 regressors per run) were introduced to account for task- and motor-related activation. Four further regressors were added to model trials in which errors were made (2 cue-locked regressors plus 2 task-locked regressors) in order to exclude them from the contrasts of interest. The resulting stimulus functions were convolved with the canonical hemodynamic response function. To account for low frequency noise a 128 s high pass filter was included; to account for serial auto-correlation, an autoregressive model was applied. All group-level effects are based on random-effects analysis.

First, contrasts of interest were computed at the group level, generating a Reward contrast (big reward > small reward), an Effort contrast (high effort > low effort) and a Delay contrast (long delay > short delay). The reversed contrasts for effort and delay were also computed, in order to test for preferential activation for low cost anticipation (low effort > high effort, short delay > long delay). The voxel-level threshold was set to 0.001 uncorrected. A whole-brain cluster-level family-wise error (FWE) correction for multiple comparison was applied, with a p-value of 0.05.

Second, we performed a conjunction between single contrasts (strict conjunction approach, Nichols, Brett, Andersson, Wager, & Poline, 2005), (big reward > small reward) & (high effort > low effort). The goal of this contrast was to test for shared neural activation in reward and effort anticipation. A whole-brain cluster-level FWE correction for multiple comparison with a p-value of 0.05 was applied to each component.

Third, in order to isolate the neural response selective to high effort, the following contrast was performed: (high effort – low effort) > (big reward – small reward). This would reveal effort-related activity, when controlling for response to reward. On the basis of previous findings, reporting a significant contribution of the brainstem nuclei in different types of effortful conditions (Boehler et al., 2011; Krebs et al., 2012; Malecek & Poldrack, 2013; Nakagawa et al., 2013; Raizada & Poldrack, 2007; Stoppel et al., 2011) and in response to high-arousal situations (Aston-Jones & Cohen, 2005), a small volume correction (SVC) for the brainstem region was applied to this contrast, to test for brainstem involvement. Within this volume, we applied a voxel-level threshold of 0.001 uncorrected, with a cluster-level FWE correction for multiple comparison (p-value 0.05). It should be noted that this was an exploratory analysis, as the current protocol would not grant sufficient spatial resolution to separate different brainstem nuclei.

RESULTS

Behavioral performance

As predicted, a repeated-measures ANOVA on the reaction times (RTs) revealed a significant interaction between condition (reward, effort, delay) and cue-type (low, high; $F_{(2, 42)} = 47.2$, $p<.001$).

Pairwise comparisons across participants revealed a significant difference in the high effort compared to the low effort condition ($t_{(21)}=6.874$, $p < 0.001$, Figure 3). In particular, subjects were significantly faster in performing easy than difficult calculations (difference of 760 ms). This confirms the effectiveness of the effort manipulation. As expected, for the delay and reward condition, no significant difference was found between the two cues (long vs. short delay, $p = 0.88$; big vs. small reward $p = 0.33$).

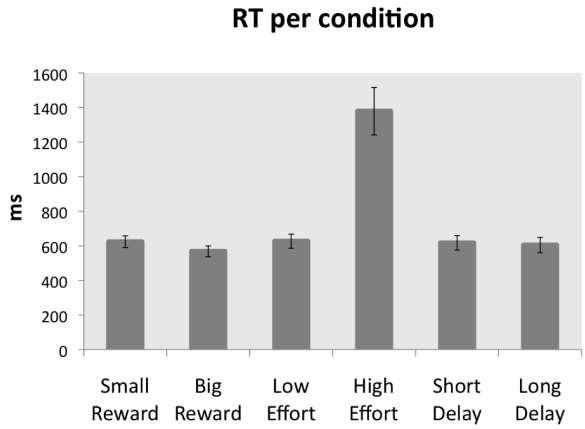

Figure 3: Average reaction times (RTs) in every condition (small reward, big reward, low effort, high effort, short delay, long delay). RT in the high effort condition is significantly higher than in the low effort condition ($p<0.001$).

Overall accuracy was very high (average 98%). In the effort block, average accuracy was also calculated for low effort (98%) vs. high effort trials (96%). This small difference was however significant ($t_{(21)}$=2.13, p=.045), confirming that the high effort trial were more difficult to perform than the low effort trials. Despite being very small, this difference might carry the potential confound of uncertainty estimation, as the chance of successful completion of a high-effort trial was slightly smaller for some participants. Although it seems unlikely that this difference in accuracy might have confounded the anticipation of effort, the dissociation between effort anticipation and uncertainty estimation should definitely be investigated in future research.

Ratings

Pairwise comparisons on the ratings about the pleasantness of the cues were performed to ensure that effort and delay costs were actually perceived as unpleasant. Indeed at the end of the experiment the participants rated the big reward cue as significantly more pleasant than the small reward cue ($t_{(21)}$ = 9.14, p<.001), the low effort cue as more pleasant than the high effort cue ($t_{(21)}$ = 6.87, p<.001) and the short delay cue as more pleasant than the long delay cue ($t_{(21)}$ = 5.53, p<.001, see Figure 4).

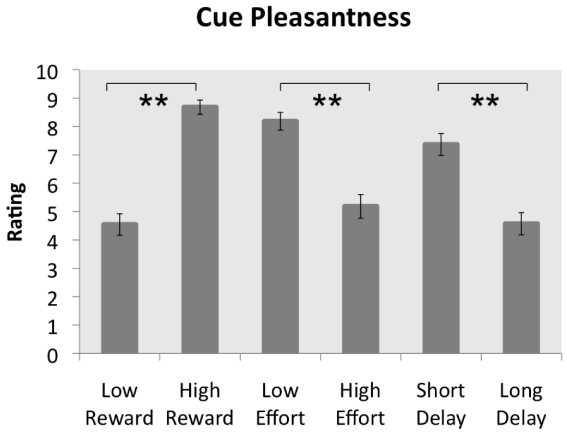

Figure 4: Average rating of pleasantness for every cue-type (small reward cue, big reward cue, low effort cue, high effort cue, short delay cue, long delay cue).

Furthermore, the pleasantness ratings for the big reward cue correlated with the reward responsiveness scale of the Bis/Bas ($r = .49$, $p < .01$), indicating that more reward-responsive participants also liked the big reward cue more.

Participants were asked to provide ratings during every break, quantifying how much attention they had paid to the cues during the previous block, on a scale from 1 to 10. The goal of these ratings was to keep participants focused on the cues. A one-way repeated-measures ANOVA on the scores with cue type as a factor (reward, effort, delay) revealed a significant difference ($F(2,42)=19.7$, $p<.001$). Pair-wise comparisons showed that participants paid more attention to the reward cues ($M=6.73$, $SD=2.08$) as compared to the delay cues ($M=4.59$, $SD=2.53$, $t_{(21)}=4.36$, $p<.001$) and to the effort cues ($M= 7.59$, $SD= 1.83$) as compared to the delay cues ($t_{(21)}=6.05$, $p<.001$). The difference between reward and effort cues was not significant (($t_{(21)}=-1.76$, $p=.09$). These ratings suggest that

while reward and effort cues were correctly attended to, overall participants paid less attention to the delay cues.

fMRI results

First, the single contrasts during the cue period were computed (see Table 1 for a summary). The Reward contrast (big reward > small reward, Figure 5a) showed significant activation in the left caudate nucleus, right anterior cingulate (ACC) and right posterior cingulate cortex (PCC). Then, anticipation of effort was addressed (high effort > low effort, Figure 5b). This contrast resulted in widespread activation, originating a cluster of 27430 voxels. Such an extended cluster-size might hamper the validity of the cluster-level inference (Woo, Krishnan, & Wager, 2014), especially concerning regional specificity. For this reason a more stringent voxel-level threshold was applied (uncorrected p=0.0001 instead of the standard 0.001). This resulted in breaking down the massive cluster in multiple clusters, thus ensuring a better localization of the significant activations.

Table 1: Summary of the activation results

Area	*Local Maxima MNI Coordinates*	*Cluster size*	*Peak T*	*cluster-level p(FWE-cor)*
Big Reward >Small Reward				
Posterior Cingulate Cortex	18 -40 34	3574	5.54	0.000
Thalamus	0 -18 18		4.31	
Inferior Parietal Cortex	-38 -28 30	598	4.33	0.001
Left Striatum	-10 14 2	290	3.78	0.026
Precuneus	6 -52 62		4.54	
Superior Frontal Gyrus	24 42 16	786	4.19	0.000
Right Striatum	22 28 2		4.12	
Anterior Cingulate Cortex	20 20 34		4.04	
High Effort > Low Effort(*)				
Left Striatum	-8 6 2	6574	6.43	0.000
Brainstem	-2 -28 -20		5.94	
Right Striatum	10 10 -2		5.86	
Right primary motor cortex	40 -2 40		5.77	
Anterior Cingulate Cortex	8 12 46		5.35	
Superior Frontal Gyrus	20 8 62		5.29	
Right Precuneus	18 -68 38	1631	5.81	0.000
Inferior Parietal lobule	32 -50 46		5.09	
Left Precuneus	-8 -72 38	543	5.57	0.000
Premotor cortex	-24 6 60	478	5.28	0.000
Left primary motor cortex	-38 6 36	358	5.19	0.000
Short Delay > Long Delay				
Orbitofrontal Cortex	-22 44 -8	243	4.75	0.047
Effort-selective contrast (SVC)				
Brainstem	-4 -32 -10	129	4.00	0.010

(*) cluster-forming threshold p=0.0001 uncorrected

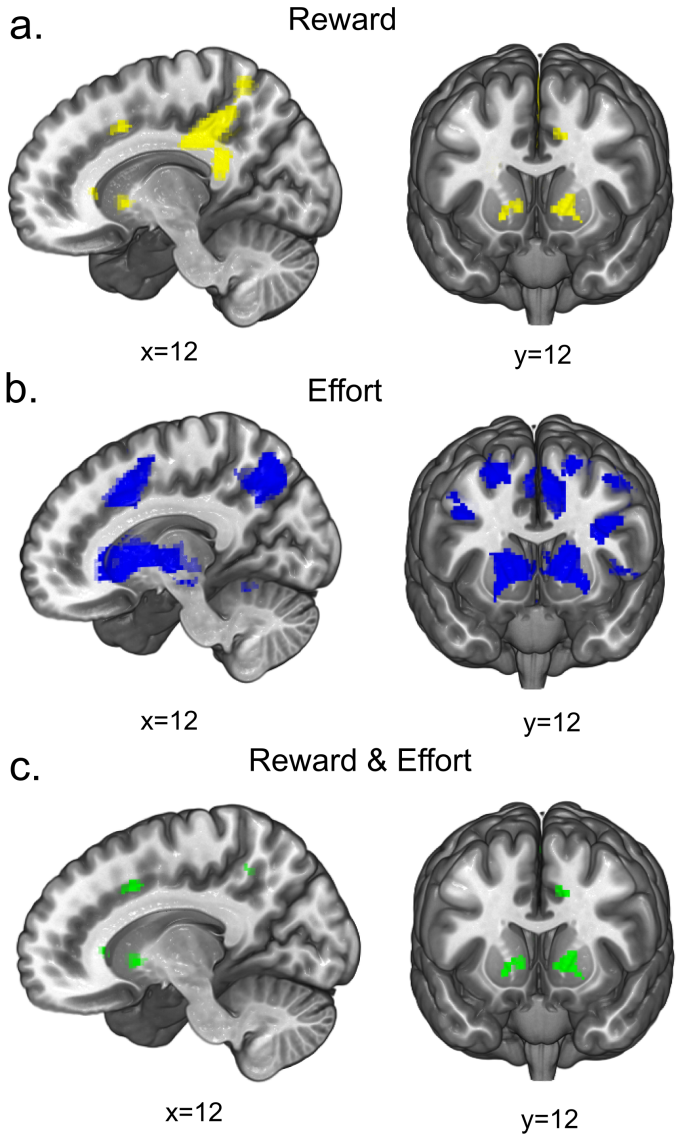

Figure 5: fMRI Results a. Reward contrast (big reward > small reward). b. Effort contrast (high effort > low effort). c. Conjunction of high effort > low effort & big reward > small reward.

Anticipation of effort significantly activated striatum bilaterally, left brainstem, right ACC, supplementary motor area (SMA), primary motor cortex bilaterally, left premotor cortex, left Insula, right superior frontal gyrus (SFG) and precuneus bilaterally. The Delay contrast (long delay > short delay) did not show any significant activation cluster surviving the whole brain FWE threshold correction.

In the reversed Effort contrast (low effort > high effort) no clusters survived the whole brain threshold. Concerning the reversed Delay contrast (short delay > long delay) the orbitofrontal cortex (OFC) proved to be sensitive to shorter delay (Figure 6).

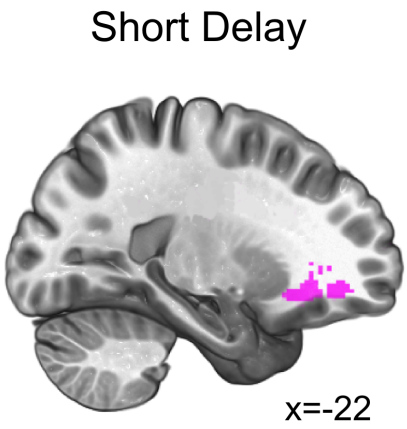

Figure 6: Short delay > long delay contrast

Second, the strict conjunction between effort- and reward-related activation ((high effort > low effort) & (big reward > small reward); incentive conjunction) revealed activation in the striatum bilaterally, the precuneus bilaterally and the right ACC (Figure 5c, see Table 2 for a detailed list).

Table 2: List of the regions resulting from the effort and reward conjunction

Conjunction
High Effort >Low Effort & Big Reward > Small Reward

Area	Local Maxima MNI Coordinates	Cluster size
	x y z	
Left Precuneus	-8 -72 38	260
Right Striatum	10 10 -2	171
Right Precuneus	8 -54 48	133
Left Striatum	-14 10 -4	97
Anterior Cingulate Cortex	12 14 40	49

As a third step, the effort-selective contrast ((high effort >low effort) – (big reward > small reward) showed a selective involvement of the brainstem in effort anticipation (Figure 6a, $T_{(21)}$= 4,00, p=0.01, SVC). No clusters at the cortical level survived. For exploratory purposes, the brainstem activated cluster was superimposed on a high-resolution proton-density averaged template normalized to the MNI space, as this sequence allows identifying the Substantia Nigra (SN, Oikawa, Sasaki, Tamakawa, Ehara, & Tohyama, 2002) thereby providing a reference for better anatomical characterization of the brainstem (Figure 7a). At visual inspection, the location of the activation cluster is not consistent with the main dopaminergic nuclei. According to the Duvernoy's atlas (Naidic et al., 2009), the location of this cluster might be compatible with other non-dopaminergic brainstem nuclei, including the serotonergic Dorsal Raphe Nucleus (DRN), or the noradrenergic Locus Coeruleus (LC). The parameter estimates for every condition for the peak voxel of this cluster are plotted in figure 7b. Paired comparisons performed on these scores revealed a significantly higher response for high effort as opposed to low Effort ($T_{(21)}$=-3.73, p=.001) and for long delay as opposed to short delay ($T_{(21)}$= 2.891, p=.009). No differential response was detected for high reward as opposed to low reward ($T_{(21)}$=-1.033, p=.313). Given

its potential theoretical relevance, this exploratory result is further discussed below, yet one should note the exploratory nature of this result. It should also be noted that the resolution of the current fMRI protocol was not optimal to distinguish between different small structures in the brainstem.

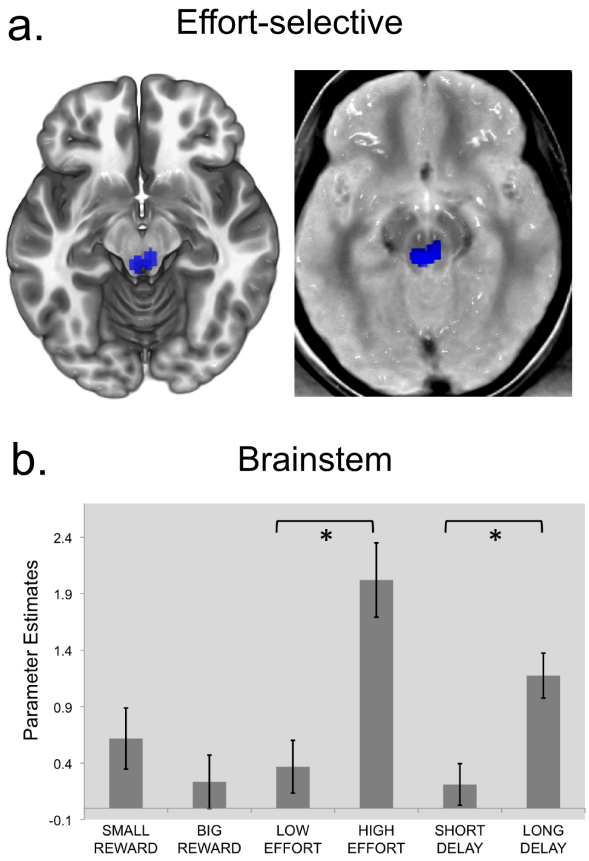

Figure 7: a. Effort-selective activation ((high effort > low effort) > (high reward> low reward)), SVC for the region of the brainstem, p value 0.05 FWE correction for multiple comparisons, plotted on Proton Density Weighted MRI Template (left image). b. Parameter estimates plot at voxel -4, -32, -10 (MNI coordinates), local maximum in the activation cluster located in the Brainstem in the effort-selective contrast.

DISCUSSION

The present study investigated the anticipation of high-level cognitive effort required to obtain a reward, while controlling for temporal confounds. Crucially, both prospective effort and reward anticipation activated the same network, involving the ACC and the striatum. This confirms the contribution of these areas to incentive-motivation and supports the essential role of this network in sustaining task-preparation for cognitive effort. The current results do not find support for a value-related encoding, according to which low effort should have elicited a stronger response. Moreover, exploratory analyses suggest a selective contribution of the brainstem to cognitive effort anticipation.

Reward-related activation (Figure 5a) was identified in the ACC and striatum, principal targets of dopaminergic midbrain projections (Haber & Knutson, 2010) and key components of reward circuitry (Amiez, Joseph, & Procyk, 2006; Kennerley et al., 2009; Liu, Hairston, Schrier, & Fan, 2011; Silvetti et al., 2013). Also, the right PCC was activated in this condition, which is known to be selectively activated by monetary gain anticipation compared to primary reinforcers (Levy & Glimcher, 2011).

The anticipation of a higher cognitive effort (Figure 5b) activated the bilateral striatum, right ACC and left brainstem, among other regions. Preparing to perform difficult calculations seems to rely on the same system that subserves other demanding cognitive functions, such as conflict monitoring (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Sohn et al., 2007) working memory encoding (Engström, Landtblom, & Karlsson, 2013), and top-down attentional facilitation (Boehler et al., 2011; Krebs et al., 2012). This converging evidence confirms the role of the ACC not only in experiencing effort (Naccache et al., 2005), but also for effort anticipation during task preparation (Hernandez

Lallement et al., 2013; Kurniawan et al., 2013; Schmidt et al., 2012). The information of an upcoming demanding task seems to act as a motivational factor needed for successful task completion. This would be in line with theoretical accounts of task preparation and task-set maintenance (Aarts et al., 2008; Luks, Simpson, Feiwell, & Miller, 2002; Sterling, 2012). This preparation effect might be mediated via dopaminergic transmission, which would be consistent with the hypothesized role of dopamine in invigorating behavior (Krebs et al., 2012; Niv, Daw, Joel, & Dayan, 2007) in effortful tasks. In the context of a task where effort is required to obtain a reward, dopaminergic release may enhance motivation for performing effortful actions, in order to overcome response cost and reap the expected benefit (Kurniawan et al., 2011). A potential mechanism is that motivational stimuli, such as the prospect of reward, boost the neuronal signal-to-noise ratio towards optimal performance (Pessiglione et al., 2007). A similar underlying mechanism might be called upon in the case of a prospective difficult task.

This interpretation finds support in animal experiments, where dopaminergic depletion induces effort avoidance (Salamone, Correa, Farrar, & Mingote, 2007; Salamone & Correa, 2012). A convergent computational framework has also been suggested by Niv et al. (2007), where dopaminergic neurotransmission would be crucial in mediating response vigor.

Dopaminergic mediation of behavioral invigoration has also been confirmed in a pharmacological study in humans (Beierholm et al., 2013). fMRI experiments in humans demonstrated the involvement of the ACC and the striatum in the anticipation of physical effort (Kurniawan et al., 2013) or perceptual load (Krebs et al., 2012). The current results show that this mechanism supports high-level cognitive effort as well, in line with what was proposed by Sohn et al. (2007).

Accordingly, ACC activity has been proven to be influenced by fatigue deriving from sustained effort in cognitive tasks (Lorist, Boksem, & Ridderinkhof, 2005). Moeller et al. (2012) showed that prolonged performance under taxing cognitive requirements is associated with decreased ACC activation and as a consequence, reduced error-related responses. This supports a key role of this region in successfully enacting cognitive effortful behavior. Interestingly, the authors also showed how this pattern is altered in cocaine-abusers, known to have abnormal dopamine levels, and how this effect can be reversed by administering a dopaminergic-agonist medication. These results together converge on the underlying dopaminergic mediation of cognitive demanding task requirements.

Interestingly, cognitive effort anticipation recruits a cortico-subcortical network that partially overlaps with reward-related regions, as shown in the conjunction analysis (Figure 5c). This confirms the hypothesized motivational effect which might reflect higher engagement induced by both the prospect of a greater benefit and the expectation of a difficult task. In this perspective, both high effort and high reward cues induce a stronger preparation effect, translated into increased neural recruitment of areas coding for incentive. For the first time, this result is shown in a high-level cognitive task, suggesting that ACC and striatum contribute to an incentive-induced resource allocation. Further converging indications are supplied by a recent study with Positron Emission Tomography (PET), that showed a correlation between dopamine release in the striatum and subjective willingness to exert effort in exchange of a reward (Treadway et al., 2012). The fronto-striatal network seems therefore to be crucial in supporting reward-driven effort exertion. The putative dopaminergic nature of this mediation is also in line with previous evidence showing the crucial influence of dopamine on high-level cognitive processes (Cools, 2011). Moreover, these findings are compatible with a recently proposed view of ACC function

(Shenhav, Botvinick, & Cohen, 2013). Here, the authors formalize the contribution of this region as estimator not only of the amount of control to be exerted (effort in our case), but also of the value of exerting control, in so far as it leads to a rewarding outcome.

In the same contrast, the precuneus was also activated bilaterally. The contribution of this region to the anticipation of both effort and reward offers interesting ground for further investigation.

Subsequently, an exploratory analysis was performed investigating selective response to cognitive effort anticipation but not to reward prospect. Given previous evidence reporting a contribution of the brainstem and theories suggesting a role for brainstem neuromodulatory systems (Aston-Jones & Cohen, 2005; Boehler et al., 2011; Krebs et al., 2012; Malecek & Poldrack, 2013; Nakagawa et al., 2013; Raizada & Poldrack, 2007), an SVC was applied for the volume of the brainstem to test for its involvement. The contrast testing selective response to effort ((high effort > low effort) > (big reward > small reward) isolated an effort-selective signal in the brainstem (Figure 7a). Definitive anatomical inference on this region cannot be performed on the current data, given the resolution constraints. It is however possible to speculate on the nature of this activation. The cluster location is not consistent with locations usually reported for midbrain dopaminergic nuclei in fMRI studies (Boehler et al., 2011; D'Ardenne, McClure, Nystrom, & Cohen, 2008; Krebs et al., 2012). The current location might be compatible with other brainstem structures, like the serotonergic Dorsal Raphe Nucleus (DRN) or the noradrenergic Locus Coeruleus (LC; Figure 7a). These hypotheses might deserve further investigation, given that previous evidence suggests a potential contribution of these nuclei in aversive processing and arousal. On the one hand, a wealth of studies demonstrated striking effects of manipulating serotonin levels on processing aversive events

(Cools, Roberts, & Robbins, 2008; Cools, Robinson, & Sahakian, 2008; Cools et al., 2005; Harmer, Mackay, Reid, Cowen, & Goodwin, 2006; Robinson, Cools, & Sahakian, 2012; van der Veen, Evers, Deutz, & Schmitt, 2007). In this perspective, expecting an upcoming effort might be considered aversive (as confirmed in our task by the ratings) and therefore rely on serotonergic midbrain input to blunt aversiveness or related behavioral reactions, and perhaps boost prefrontal activity needed for accurate task performance (Amat et al., 2005; Bromberg-Martin, Hikosaka, & Nakamura, 2010; Sterling, 2012). On a convergent note, theoretical and computational frameworks of cost and benefit encoding have assigned a putative function to serotonergic modulation (Boureau & Dayan, 2011; Cools, Nakamura, & Daw, 2011). On the other hand, anticipating higher effort might induce an arousal response and therefore elicit noradrenaline release (Aston-Jones & Cohen, 2005; McClure, Laibson, Loewenstein, & Cohen, 2004), thus suggesting that the present functional result would reflect putative LC-noradrenergic activity. Convergent evidence for a putative LC contribution during demanding tasks was also provided by Raizada and Poldrack (2008). At the current stage, both hypotheses are rather speculative. This result might however be informative and fruitful ground for further investigation.

As for the additional experimental condition, the delay manipulation, the expectation of a short delay (short delay > long delay, Figure 6) revealed a value-related signal in the orbitofrontal cortex, consistent with evidence from delay discounting studies (McClure et al., 2004; Tanaka et al., 2004). No significant activation was elicited by the prospect of a longer delay. The exploratory analysis on the brainstem activation however, shows a stronger response in that region not only for greater efforts, but also for longer delays (Figure 7b). With the caveat of the localization limitation, it is worth nothing that a critical involvement of the DRN in delay discounting has been recently shown in rats, where serotonergic

activity seems to facilitate waiting for a benefit (Miyazaki, Miyazaki, & Doya, 2011), and to be necessary to tolerate longer delays (7-11 seconds) (Miyazaki, Miyazaki, & Doya, 2012). Additional evidence is accumulating supporting the hypothesis of serotonin involvement in promoting a more foresighted reward evaluation in both animals and humans (Luo, Ainslie, Giragosian, & Monterosso, 2009; Schweighofer et al., 2008; Schweighofer, Tanaka, & Doya, 2007; Tanaka et al., 2004). Considering the methodological limitations of the current experiment, this might be fruitful venue for future research.

CONCLUSIONS

This study provides the first evidence for a shared motivational effect induced at the neural level by both reward prospect and the anticipation of cognitive effort in complex cognitive tasks. This is associated with activation in the ACC and the striatum, supporting behavioral engagement and resource-recruiting towards a final goal. Moreover, an exploratory analysis identified an effort-selective signal in the human brainstem, which suggests potential contribution of non-dopaminergic brainstem nuclei to effort anticipation.

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CHAPTER 4
CHOOSING TO MAKE AN EFFORT AND PREPARING TO OVERCOME IT: THE ROLE OF THE ANTERIOR CINGULATE CORTEX [1]

Benefits typically come with an effort cost. Anticipating potential rewards and effort requirements are essential skills in driving adaptive behavior. However, the underlying neural mechanisms are still debated. A net-value account has been proposed, according to which the value of the reward is discounted by the required effort. This computation would be implemented by the Anterior Cingulate Cortex (ACC). However, this theory has been recently challenged by incompatible results, showing motivational encoding of effort in the ACC instead, where activity in this region is essential in prompting and sustaining effortful behavior towards a goal. The purpose of the current study was to directly test the divergent predictions arising from these accounts, incorporating a crucial factor: decision-making. Previous studies did not differentiate between effort-related decision-making and anticipation of effort when no choice was required. Given the contribution of ACC to decision-making, controlling for this factor is crucial to disentangle effort encoding in the ACC. To this end, a cognitive effort fMRI paradigm was implemented, consisting of two phases: a decision-making phase and a performance phase. This allowed to systematically investigate effort encoding during decision and anticipation in the same subjects. The results support the motivational account, showing increased ACC activity as a function of required effort, across both phases. A targeted ROI analysis revealed a modulation of phase, showing an inverted U-shaped relationship between effort encoding during decision and ACC activity in the low reward condition. This suggests a role of ACC in prompting engagement in effortful behavior only when this is considered worthwhile.

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[1]Vassena E., Botvinick M.M., Krebs R.M., Silvetti M., De Loof E., Fias W. & Verguts, T., Choosing to make an effort and preparing to overcome it: the role of the Anterior Cingulate Cortex. Manuscript in preparation

INTRODUCTION

When faced with an effortful and potentially rewarding task, animals try to maximize utility (Walton et al., 2006; Schweimer and Hauber, 2010), taking both benefits and associated costs into account. For example, rats choose to climb a barrier only when this leads to more food pellets than for an easier available option (Salamone et al., 2007; Salamone and Correa, 2012). Maximizing utility drives human behavior as well (Kahneman and Tversky, 1979). People find effort per se aversive (Kool et al., 2010), showing a tendency to avoid it, in favor of easier options. However, when a potential gain is available, the willingness to exert effort increases as a function of it (Prévost et al., 2010; Westbrook et al., 2013). When the gain is considered worth the effort, a preparation process is prompted which mobilizes the resources needed for successful task completion (Mulert et al., 2005; Kouneiher et al., 2009).

A number of studies investigated cost-benefit computations and resource mobilization. A pivotal role for cost/benefit computation is assigned to cortico-subcortical interactions mediated via dopaminergic (DA) transmission (Phillips et al., 2007). A main cortical station is the Anterior Cingulate Cortex (ACC). In vivo electrophysiology in primates showed how ACC neurons encode different features of relevant stimuli, including reward prediction error (i.e. unexpected receipt of omission of a reward, Amiez et al., 2006; Matsumoto et al., 2007) action values (i.e. potential reward associate with a particular action, Rudebeck et al., 2008), probability, and required effort, Kennerley et al., 2011). All these features can be integrated in a net-value signal, which encodes the benefit (i.e. reward) discounted by the costs implied in obtaining it.

In humans, net-value signals have been identified in the ACC and in the striatum at difference stages of effort-demanding behavior. Croxson et al. (2009) showed in cancellation task a stronger ACC and striatum activation when subjects viewed a cue anticipating a high reward requiring low effort (i.e. smaller number of dashes to be clicked on to complete the task). However, in this task the more effortful condition was associated with longer execution time, thus implicating a potential delay confound in the value computation process. Botvinick et al. (2009) reported an increased response in the ventral striatum at reward delivery for a high reward, obtained with low effort (i.e. higher overall net-value). Prevost et al. (2010) showed that activation in the ACC and ventral striatum was also associated to subjective value attributed to cues anticipating physical effort, to be exerted to get to see erotic pictures. In this last study however, striatal activity encoded subjective value of the cue (with higher activity for higher net-value), while ACC activity was associated with the anticipation of higher effort requirements (lower net-value).

The result from Prevost et al. already sheds doubt on the generality of the net-value coding in ACC. In fact, a series of studies in animals and humans challenged the theory that ACC is solely dedicated to net-value computation. Instead, they favor a motivational account, according to which ACC activity sustains anticipation and exertion of effort. For example, in rodents, inactivation of the ACC induces effort avoidance (Walton et al., 2009), even when general appetitive behavior is preserved. Vascular or neoplastic lesions in humans can lead to clinical conditions, such as akinetic mutism (Devinsky et al., 1995) and other disorders, where initiation of motivated behavior is impaired (Wacker et al., 2009; Njomboro et al., 2012; Rive et al., 2013).

In terms of functional activation, the motivational account predicts increased ACC activation for the anticipation of higher effort, in sharp contrast with the net-value account, which instead predicts lower ACC activation for higher effort. Recent fMRI studies found preliminary support for the motivational account, showing increased ACC activity when anticipating higher physical and cognitive effort (Krebs et al., 2012; Schmidt et al., 2012; Kurniawan et al., 2013; Vassena et al., 2014). In some instances, the same motivational effect was also induced when the prospect of a higher reward was anticipated (Krebs et al., 2012; Vassena et al., 2014). According to this line of results, ACC implement the initiation and energizing of goal-directed actions.

Recent computational accounts of ACC function are formulated in the framework of the net-value perspective. In these frameworks, the ACC is implemented as a critic (in the context of an actor-critic architecture, Sutton and Barto, 1998), that is a unit keeping track of the value associated with certain stimuli in the environment, formulating predictions and updating these predictions on the basis of outcomes (Alexander and Brown, 2011; Silvetti et al., 2011). A different line of recent theories of ACC function seems to be compatible with a motivational account instead. Holroyd and Yeung (2012) hypothesize the ACC to be the locus of maintenance of behavioral policies (i.e. sequences of actions towards a goal), in the framework of hierarchical reinforcement learning theories (Botvinick et al., 2009b). Weston (2012) suggests this region to be crucial in anticipating contingent "requirements" (i.e. mobilizing resources in response to needs). Sterling (2012) proposes a role for ACC in predictively preparing for environmental challenges in order to maintain homeostasis.

To sum up, from both empirical and theoretical lines, two dominating views emerge in interpreting ACC contribution to decision making and motivated behavior, one favoring a net-value perspective, and the other favoring a motivational account. The primary goal of the current study was to address the divergent predictions arising from these accounts. As reported above, a net-value perspective predicts decreased ACC activity for higher effort (i.e. higher costs entails lower net-value), while a motivational account predicts increased ACC involvement for higher effort. However, one major issue characterizing previous studies was that decision-making phase was not explicitly manipulated. Some of the aforementioned paradigms involved making a series of choices between options offering different combinations of reward and effort demands. Others examined cue-locked activation instead, where only one option was available. These different conditions might dramatically affect net-value computation and motivation-related processes, and might (at least partially) account for the contradictory results. Indeed, net-value computation might be primarily called upon when a choice is possible, while upcoming but inevitable effort might prompt motivation-related processes. Moreover, outside the effort domain, ACC activity is commonly associated with making a choice between different available options (Brass and Haggard, 2007). Testing for the modulation of decision making on effort encoding seems therefore mandatory, to better specify both effort encoding and decision-making processes.

To address these issues, a two-phase task was implemented, systematically investigating effort-related decision making and anticipation of effortful performance. The goal was to measure ACC response using fMRI, in the same task in the same subjects and using the same visual stimuli for both phases (decision making and anticipation). We examined the

type of encoding (net-value vs. motivational) and tested if this was modulated by phase (decision-making vs. anticipation). Moreover, this allowed to test for a shared neural encoding across phases. Additionally, the experiment was designed to overcome the categorical dichotomy easy vs. hard, by investigating parametric effort encoding. This allowed to test for a possible modulation of phase on encoding type, and for the linear nature of this modulation.

MATERIALS & METHODS

Participants

Twenty-three healthy volunteers participated in this experiment (10 males), with a mean age of 21 (range 19-25). The experimental protocol was approved by the Ethical Committee of the Ghent University Hospital. All participants signed an informed-consent form before the experiment. They filled in a safety checklist as well, to exclude contraindications, as well as neurological or psychiatric conditions.

Experimental procedure

An fMRI experimental design was implemented, consisting of a decision-making phase and a performance phase of the same task. In the decision-making phase, participants received a number of cues, that they could accept or reject. In the performance phase, participants had to perform the actual task. Before the scanning session, the participants were trained to familiarize them with the stimuli and the experimental procedure (Figure 1). The training also consisted of two parts. The first part entailed exposure to the decision-making phase to learn the meaning of the cues. The second part

was a short version of the performance phase, to have the participants experience all the possible effort levels of the task. The effort manipulation was induced by means of arithmetic operation (see below for details). Only in this performance-training phase, after every trial participants had to rate how difficult and how pleasant they found each trial upon completion.

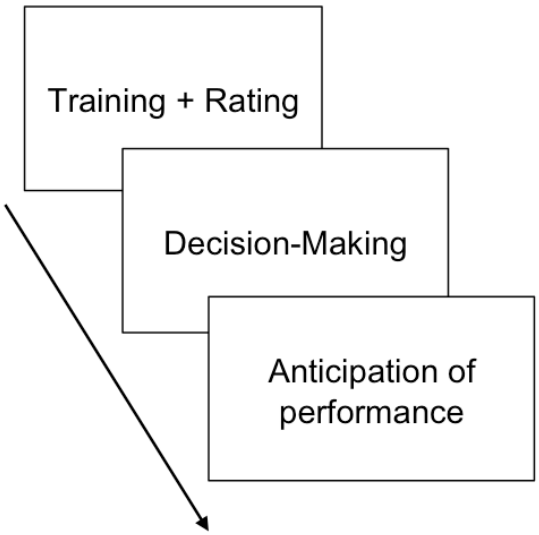

Figure 1: Experimental procedure. Participants undergo a training phase, familiarizing with both decision-making phase and anticipation of performance phase. During the training, they are also ask to rate every trial concerning experienced difficulty and pleasantness. Subsequently, in the scanner they perform the decision-making phase, followed by the anticipation of performance phase

In both phases, each trial started with a cue (a grey circle, displaying a grid of 4 by 2 lines, on which two lines were black). Every cue indicated a combination of a certain degree of effort (horizontal lines, 4 possible difficulty levels) and a certain amount of reward (vertical lines, low reward of 20 cents or high reward of 40 cents). This resulted in 8 possible cues (4 by

2, see Figure 1b). One more cue was included, the reference cue (same circle, without black lines). The reference cue would grant the lowest reward possible (5 cents) at the lowest effort possible (lower than the other 4 levels).

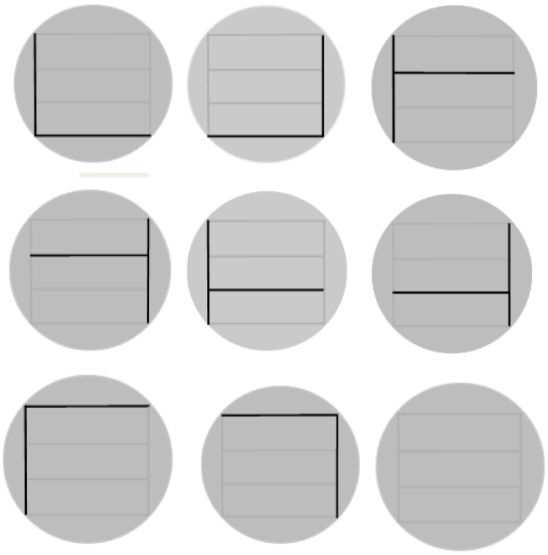

Figure 2: Cues. Each cue represents a combination of effort and reward. Horizontal black lines indicate effort level (from 1 to 4). Vertical black lines indicate reward (low/high). The cue with no black line is the reference cue (lowest effort/lowest reward).

This reference cue was introduced in both phases to make sure that its appearance in the performance phase would not be unexpected in any possible choice-strategy scenario (i.e. if the participants always accepted the more difficult option). Participants were alerted that the reference cue would sometimes be presented in the decision-making phase, and that in this case their choice (accept vs. reject) would not be relevant, as they would receive the reference cue anyway. In both decision-making and performance phases, the cue was preceded by a randomly jittered interval ranging from 2000 to

4000 ms (mean 3000 ms) and followed by a variable interval ranging from 600 to 9000 ms, jittered in a pseudo-exponential fashion (mean 4000 ms).

The decision-making phase contained 126 trials, each consisting of a series of choices (Figure 3). At the beginning of each trial one of the cues was presented, and the participant had to accept or reject this particular cue (i.e. this combination of prospective effort and potential reward). Importantly, first the cue was presented, and only after the jittered interval a response display would appear, showing the two options "accept" and "reject". The position of the options was randomized across trials and the participants had to produce a left or right response, depending on the location of the desired answer. The goal of this procedure was to disentangle the decision-phase from response preparation processes.

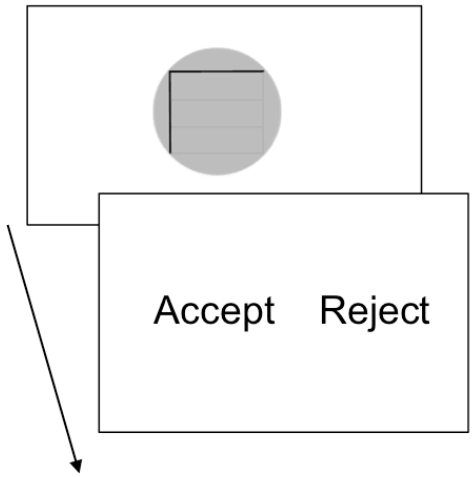

Figure 3: Decision-making phase. Participants are presented with all the cues. Per every cue, they have to decide to accept or reject. If they accept, they are told they will receive a trial corresponding to that cue in the performance phase.

Rejecting the current cue would mean automatically receiving the trial type associated with the reference cue (lowest effort and lowest reward possible). Participants were told that their chosen cues would determine the actual trials (i.e. combined reward and difficulty level) to be performed in the performance phase. To avoid disengagement in both tasks, they were also told that errors during the performance phase would cause a loss, corresponding to the amount of money at stake in the current trial. At the end of the decision-making phase, the experimenter communicated that only a percentage of the trials in the performance phase would correspond to the actual choices from the decision-making phase. The remaining trials would be randomly selected by the computer for experimental reasons (i.e. in order to make data from different participants comparable). The goal of this procedure was to administer the same performance task to all participants. None of the participants expressed complaints about this communication.

In the performance phase, the same number of trials (126 trials) and the exact same cues (but in different random order) as the decision-making phase were presented (Figure 4). This aimed at making the decision-cue (decision-making phase) and the performance-cue (performance phase) as comparable as possible. In this phase, each trial started with the cue, indicating the upcoming effort level and the reward to be obtained in case of correct answer. The cue was followed by a series of 4 calculations, formed by single-digit numbers flashing on the screen. Each effort level corresponded to an operation implying decade crossing (e.g., 7+8=15). Decade crossing requires carrying or borrowing, which is more difficult than not crossing (e.g. 7+2=9; Imbo et al., 2005). The calculations were followed by a response display, showing two possible results among which the participant needed to select the correct response within 500 ms.

Subsequently, the feedback would be displayed (the obtained reward, or the loss in case of error).

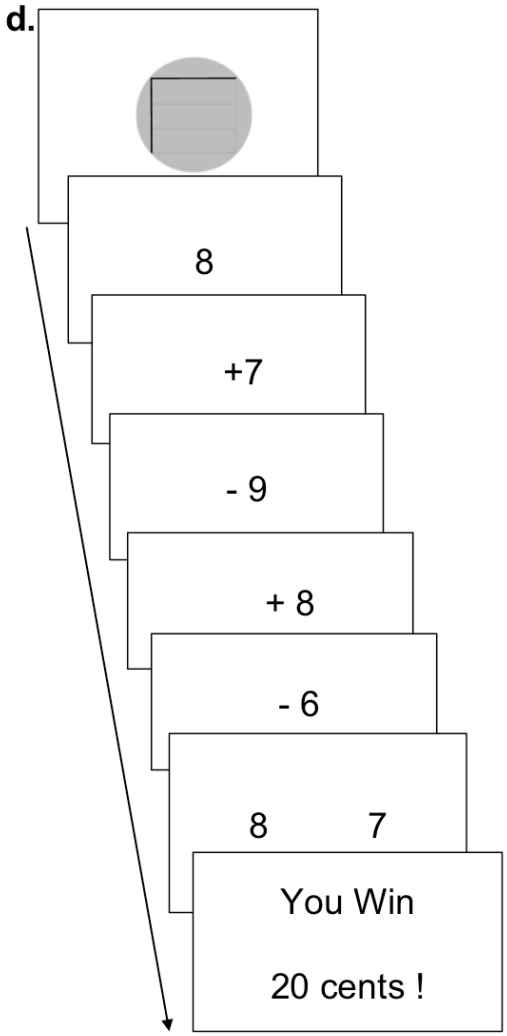

Figure 4: Anticipation of performance phase. Each cue is presented, now followed by a calculation of the correspondent effort level. Participants are suppose to calculate the result on line, and pick the correct response. After the response, they receive feedback.

At effort level *n*, there were *n* decade crossings (e.g., 2 at effort level 2). This procedure resulted in a parametric manipulation of effort (four levels, from 1 easy, to 4 hard), which allowed testing for this type of neural encoding. Importantly, the implementation of the calculation task was preceded by a behavioral piloting phase, to tune the overall difficulty guaranteeing an overall accuracy above 90%. In this way, we ascertained querying effort anticipation rather than risk estimation.

Behavioral data analysis

The performance-training phase included 15 trials (3 trials per difficulty level (3*4=12) plus 3 reference trials). After completing each trial, the participant had to rate the trial on experienced difficulty and experienced pleasantness, both on a scale from 1 to 7. These ratings were analyzed as a manipulation check. The goal was to ensure that trials entailing higher effort would be perceived as more effortful and less pleasant (Kool et al., 2010). A linear regression model was fitted to the difficulty ratings of each participant separately, with effort level (1-4) as a predictor of perceived difficulty. Subsequently a one-sample t-test was performed on the regression coefficients, to test the effect at the group level. The same analysis was performed on the pleasantness rating dependent variable.

During the decision-making phase participants could choose which options to accept or reject. Hence, it was possible to analyze choice behavior as a function of the effort level and the potential reward offered by the cue. A multiple logistic regression model was fitted per every participant, with effort and reward as predictors of choice (acceptance of the cue). A one-sample t-test was then performed across the group coefficients. To analyze choice reaction times (RTs), a multiple linear regression was performed for

each participant separately, with effort and reward as predictors. A one-sample t-test was then performed across the group coefficients. Average acceptance rate and choice entropy were computed for every condition. A repeated-measure analysis of variance (rANOVA) was performed on the average percentages of acceptance, with effort and reward as factors. Choice entropy was also calculated for every condition, as a measure of uncertainty in the choice behavior (Shannon entropy, calculated as $-p \log2 (p) - (1-p) \log2(1-p)$, where p is the probability of accepting a particular cue, Shannon, 1948). A rANOVA was performed on the average entropy, with effort level and reward as factors. Moreover, choice entropy gives information about choice-style of the participants, thus allowing inter-individual differences analysis. This is especially relevant when testing effort encoding in the ACC, as this region as been associated to choice conflict (Botvinick et al., 2004). Excluding choice entropy encoding would be a stronger indication in favor of effort encoding.

Finally, the behavioral data from the performance phase were analyzed. Accuracy and RTs were calculated in every condition. Both accuracy and RT data were then subjected to rANOVAs, with effort and reward as factors.

fMRI data acquisition

Data was acquired using a 3T Magnetom Trio MRI scanner (Siemens), using a 32-channel radio-frequency head coil. First, an anatomical T_1 weighted MPRAGE sequence was collected, resulting in 176 high-resolution slices (TR = 1550 ms, TE = 2.39, slice thickness = 0.9 mm, voxel size = 0.9 x 0.9 x 0.9 mm, FoV = 220 mm, flip angle = 9°).

Subsequently, functional images were acquired using a T_2* weighted EPI sequence (33 slices per volume, TR = 2000 ms, TE = 30 ms, no inter-slice gap, voxel size = 3 x 3 x 3mm, FoV = 192 mm, flip angle = 80°). On average 510 volumes were collected during the decision-making phase, and 1180 volumes during the performance phase.

fMRI data analysis

The first 4 volumes of the functional scans were discarded to allow for steady-state magnetization. The data were preprocessed with SPM (http://www.fil.ion.ucl.ac.uk/spm). Images were realigned to the first image of the run. The structural T_1 image was coregistered to the functional mean image to allow a more precise normalization. The unified segmentation and nonlinear warping approach of SPM8 was applied to normalize structural and functional images to the MNI template (Montreal Neurological Institute). Functional images were then smoothed with a Gaussian kernel of 8 mm full width half maximum (FWHM).

Subsequently the General Linear Model (GLM) approach was applied in order to identify each subject's condition-specific activation. Two different first-level GLMs were set up per every participant, one modeling the decision-making phase and one modeling the performance phase. In the decision-making model, 18 event-related regressors of interest were introduced, 9 regressors to model the cues (8 cues for the different effort/reward combinations plus one reference cue) plus 9 regressors to model the response in each condition (when the participants pressed the key to accept or reject the cue). Six more regressors were introduced in the model to account for motion-related activity. In the performance model, 27 event-related regressors of interest were introduced, 9 regressors to model

the cues (as in the decision-making model, one per condition), 9 regressors to model task-related activation (from task onset to response display onset, separately modeled per every condition), and 9 regressors to model the feedback (also separately modeled per condition). Two additional regressors were added to account for the short break periods (covering the duration of the break) and for the trials where errors were made (covering the entire trial length), which were then excluded from the analysis. As in the decision-making phase, 6 motion-related regressors were also added.

At the second level, we focused on cue-related activation. As a first step, a random-effect analysis was performed on both phases separately, by implementing two 4 x 2 factorial designs, with effort (level from 1 to 4) and reward (low vs. high) as factors. Subsequently a parametric contrast for the effort factor was computed in both models, to identify areas encoding effort in a parametric fashion in both decision-making and performance phase. To each contrast, a voxel-level threshold of p=.001 uncorrected was applied, and cluster-level family-wise error (FWE) correction for multiple comparisons with a p-value of 0.05. On the resulting images, a conjunction analysis was performed (Nichols et al. 2005), to identify potentially shared neural substrate in effort encoding across decision-making and performance phase.

As a second step, the a priori hypothesis of ACC involvement was investigated in a targeted Region of Interest (ROI) analysis. The ACC ROI was defined on the basis of a previous study on effort processing (Botvinick et al., 2009a, figure 3a), guaranteeing unbiased selection. This resulted in a sphere with a 10 mm radius, centered on the MNI coordinates x=2 y=21 z=40 (see figure 2). Condition-specific activation (percent signal change) was extracted separately for decision-making and performance phase using

the MARSBAR toolbox (Brett et al., 2002) and submitted to a repeated-measures analysis of variance. The goal of this analysis was to better specify the role of ACC in effort and reward encoding in both phases.

Finally, a further manipulation check was performed by analyzing task-related activation during the performance phase (task-regressor from task onset to response). A random-effect analysis was performed by implementing a factorial design with effort level and reward as factors. The parametric contrast for effort was calculated, to investigated neural activation during the task as a function of effort. The negative parametric contrast for effort was also computed, to identify regions showing decreased activation for increased task effort.

RESULTS

Behavioral results

First, the ratings collected during the performance-training phase were analyzed. Despite the limited sampling of this phase (only 15 trials), it was still possible to test the subjective perception of the different effort levels, as a manipulation check. One participant had to be excluded from this analysis, as he/she picked always the same rating per every level. Participants reliably experienced higher effort trials as more difficult (regression coefficient of effort, $t_{(21)}= 7.17$, $p<.001$) and less pleasant ($t_{(21)}= -4.18$, $p<.001$). Hence, the effort manipulation was successful.

Second, the choice data from the decision-making phase were analyzed. Participants accepted less often the more difficult cues ($t_{(22)}= -4.19$, $p<.001$) and more often the high reward cues ($t_{(22)}= 4.69$, $p<.001$). This

suggests that participants correctly focused on the cues in the decision-making phase, as both manipulated factors influenced choice behavior. The overall acceptance rate for the proposed cue was 67.39 % (± 12.9, Figure 5). Both effort and reward levels showed a significant main effect on the average acceptance rate per condition (effort $F_{(3,66)}$=71.06, p<.001, reward $F_{(1,22)}$=37,73, p<.001, see Figure 5), as well as interaction ($F=_{(3,66)}$=13.25, p=<.001).

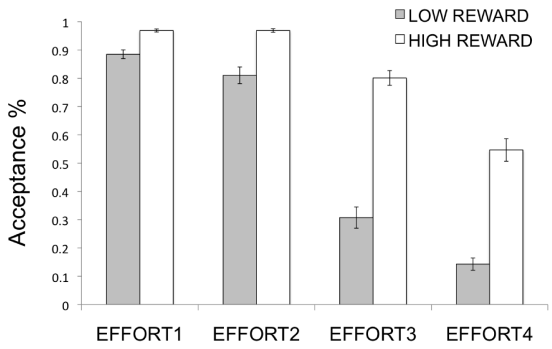

Figure 5: Average acceptance rate is reported per every effort level (x-axis) and reward (grey = low, black = high).

Choice entropy was also calculated as a measure of uncertainty in choice behavior. This was computed per every cue and then averaged across participants (Figure 6). Choice entropy was significantly influenced by effort ($F_{(3,66)}$=4.25, p=.008). Importantly, the interaction effort by reward was also significant ($F_{(3,66)}$=4.18, p=.009). Therefore a rANOVA was run separately for low and high reward, showing a significant effect of effort on choice entropy only in the high reward condition ($F_{(3,66)}$=10.86, p<.001). No difference in choice entropy for low reward was reported ($F_{(3,66)}$=.06, p=.98).

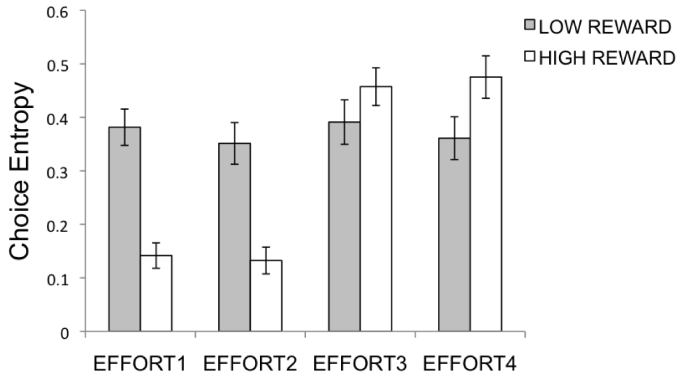

Figure 6: Average choice entropy is reported per every effort level (x-axis) and reward (grey = low, black = high).

Finally, the behavioral data from the performance phase were analyzed. The overall accuracy was very high as planned (92,37 % ± 5,05). There was a main effect of effort on accuracy ($F_{(3,66)}$=6.82, p=<.001) and no effect of reward ($F_{(1,22)}$=.06, p=.81). This confirms that higher effort trials were consistently more difficult to perform. It is important to note however, that average accuracy was still high in every effort level, suggesting that the relevant factor is effort rather than risk. RTs showed a significant, albeit small, effect of effort ($F_{(3,66)}$=14.31, p=<.001), mean difference between effort level 1 and 4 of 53 ms). This further confirms the successful effort manipulation. The maximum response time was 500 ms, above which the trial would be considered as an error. This short time window to respond might account for the small size of the effect on RTs and the more prominent effect on accuracy. Reward had no effect on RTs ($F_{(1,22)}$=1.00, p=.33). These results, taken together with the ratings collected during the training, confirm the efficacy of the effort manipulation.

Whole-brain cue-related fMRI results

A comprehensive summary of the activation results is reported in Table 1. At the cue in the decision-making phase, the parametric contrast for effort activated the ACC and the Precuneus (see figure 7a). In other words, these areas were increasingly activated for cues indicating more effortful options, thus showing a motivational encoding. No significant clusters were reported in the reversed parametric contrast (which would highlight areas increasingly activated for lower effort), thus providing no evidence in favor of a net-value encoding. The reward contrast (high reward > low reward) activated the extrastriate cortex (see figure 7d).

At the cue in the performance phase, the parametric contrast for effort activated the ACC, the striatum bilaterally, the right Superior Frontal Gyrus (SFG), the Supplementary Motor Area (SMA), the precentral gyrus, the Posterior Cingulate Cortex (PCC), the orbital part of the Inferior Frontal Gyrus (IFG), the extrastriate cortex, the right Angular Gyrus (AG) and the Inferior Parietal Lobule (IPL, see figure 7b). The reward contrast (high reward > low reward) activated the cuneus, the extrastriate cortex, the precentral gyrus and the Superior Parietal Lobule (SPL, figure 7e). The reverse parametric (increased activation for lower effort) contrast for effort did not elicit any significant activation.

A conjunction analysis was performed on the parametric effort contrasts from the decision-making cue and the performance cue. This yielded overlapping activation in the ACC and in the Precuneus (see figure 7c, Table 2).

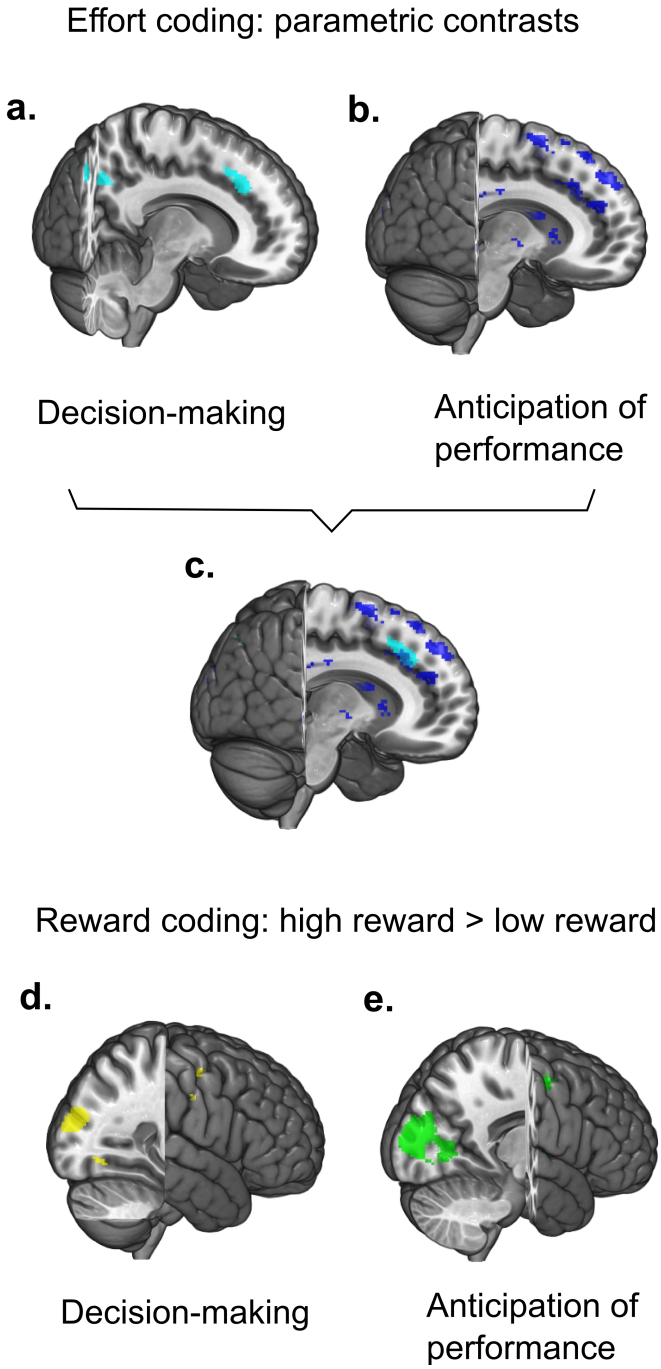
Effort coding: parametric contrasts
a.
b.
Decision-making
Anticipation of performance
c.
Reward coding: high reward > low reward
d.
e.
Decision-making
Anticipation of performance

Figure 7: Whole-brain activation results. a. Cue-locked parametric effort contrast during the decision-making phase (light blue clusters). b. Cue-locked parametric effort contrast during the anticipation of performance phase (blue clusters). c. Conjunction analysis showing the overlap between the effort parametric contrasts during decision making (light blue) and anticipation of performance (blue). d. Reward contrast (high reward > low reward) during the decision-making phase (yellow clusters). e. Reward contrast (high reward > low reward) during the anticipation of performance phase (yellow clusters).

Table 1: Summary of the activation results

Area	*MNI Coordinates x y z*	*cluster-level FWE*	*cluster-level FDR*	*cluster size*	*peak T*
Decision-Making Phase					
Parametric contrast for effort					
Precuneus	6 -66 36	0.044	0.017	205	4.12
	18 -60 34				3.44
ACC	10 30 34	0.019	0.017	260	4.07
	2 20 42				3.68
Reward contrast (high reward>low reward)					
Occipital cortex	18 -94 16	0.000	0.000	537	5.52
	26 -94 20				5.19
	20 -78 -4				4.03
Anticipation of Performance Phase					
Parametric contrast for effort					
Occipital cortex	16 -94 16	0.000	0.000	4058	6.63
	-8 -98 6				6.04
	-6 -76 4				4.82
Right superior frontal gyrus	22 52 16	0.000	0.000	1371	5.31
ACC	12 28 32				3.90
Inferior frontal gyrus	-24 18 -14	0.000	0.000	913	5.15
	-30 8 24				4.30

Putamen	-18 10 -4				4.03
Mid-cingulate cortex	-2 -18 34	0.001	0.002	531	5.12
	-6 -38 26				4.10
	8 -36 28				3.76
Caudate	16 18 -6	0.001	0.002	532	4.46
Putamen	24 -4 8				3.82
	16 4 10				3.78
Postcentral gyrus	-38 -30 32	0.003	0.004	448	4.43
	-36 -18 30				4.39
	-38 -10 28				3.76
Precentral gyrus	48 -16 28	0.004	0.005	423	4.39
	50 -2 40				4.09
Postcentral gyrus	54 -18 40				3.58
Supplementary motor area	-2 -6 62	0.004	0.005	416	4.14
	4 0 66				3.99
	6 12 60				3.44
Angular gyrus	38 -58 36	0.007	0.008	369	4.07
Inferior parietal lobule	32 -54 48				3.69
Reward contrast (high reward>low reward)					
Cuneus	16 -92 8	0.000	0.000	1164	7.91
Occipital cortex	24 -92 18				6.18
	16 -70 2				3.95
Precentral gyrus	-44 -8 50	0.006	0.005	378	4.48
	-36 -14 40	0.007			3.62
Superior parietal lobule	-28 -60 52	0.007	0.005	365	4.01
	-14 -64 64				3.89

Table 2: List of the regions showing overlap in the conjunction contrast

Area	*MNI Coordinates x y z*	*cluster size*	*peak T*
Conjunction contrast			
Parametric contrast for effort during decision-making & anticipation of performance			
Precuneus	8 -72 38	67	4.06
	14 -64 36		3.51
ACC	12 28 32	54	3.90

fMRI cue-related ROI analysis results

The percent signal change (psc) per every condition in both decision-making and performance phase is reported in Figure 9 and Figure 10. The goal of this analysis was to further characterize the involvement of the ACC in effort estimation, especially targeting the type of encoding (net-value vs. motivational).

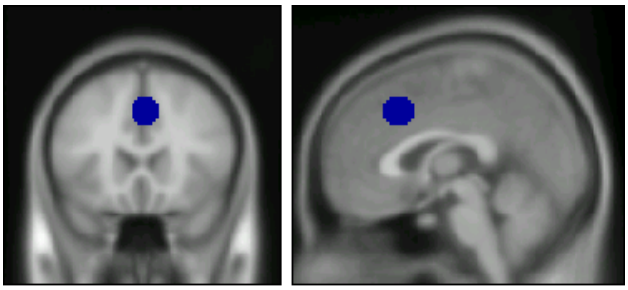

Figure 8: Region of Interest (ROI) in the ACC from Botvinick et al. (2009).

In the decision-making phase, the whole-brain contrast had revealed a parametric encoding of effort in a motivation-related manner, where increased activation was associated with higher effort demand. No evidence for a net-value encoding was reported. Interestingly, the ROI analysis revealed dissociable patterns for high vs. low reward condition. Effort encoding is indeed linearly increasing in the ACC as a function of effort level only the high reward condition (Figure 9). In the low reward condition however, this monotonic increase only reaches effort level 3, then decreasing again for effort level 4. This inverted U-shaped pattern is confirmed by an effort by reward interaction ($F(3,66)=4.85$, $p=.004$). A main effect of effort ($F_{(3,66)}=3.39$, $p=.02$) and reward ($F_{(1,22)}=4.97$, $p=.04$) were also reported in this area. When only the low reward condition was included in the analysis, the main effect of effort was only marginally significant ($F_{(3,66)}=2.71$, $p=.05$),

but a significant quadratic trend was reported ($F_{(1,22)}$=9.47, p=.006), confirming again the inverted-U shaped trend.

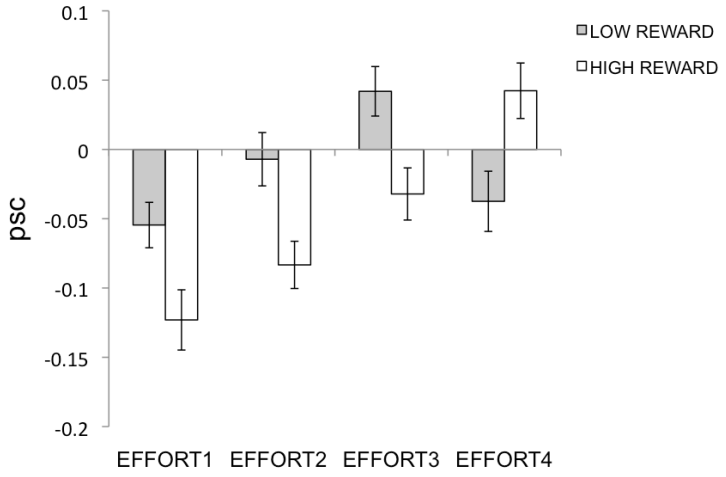

Figure 9: Percent signal change (psc) during decision-making in the four effort levels (x-axis) and two reward levels (grey=low reward, white=high reward).

In the performance phase, the whole-brain parametric contrast equally showed linear encoding for effort in a motivational-related fashion. Similarly, no indication for a value-related encoding was reported. In this case, the percent signal change extracted from the ROI confirmed that the trend was linear for both low reward and high reward conditions (Figure 10), showing a main effect of effort level ($F_{(3,66)}$=3.25, p=.02) and no effect of reward ($F_{(1,22)}$=.36, p=.56) nor an interaction ($F_{(3,66)}$=.60, p=.62).

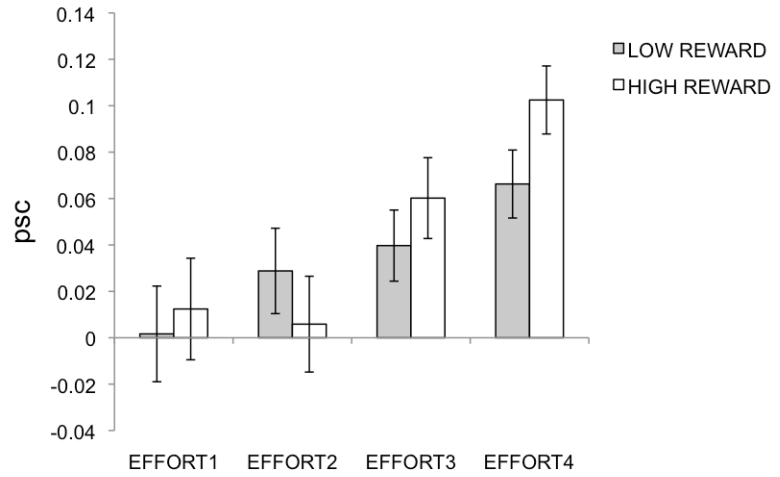

Figure 10: Percent signal change (psc) during anticipation of performance in the four effort levels (x-axis) and two reward levels (grey=low reward, white=high reward).

fMRI task-related results

The goal of this analysis was a further manipulation check, that is checking neural activation during task performance in the performance phase as a function of required effort. The parametric effort contrast revealed increased activation for increased effort in ACC, striatum, Dorsolateral Prefrontal Cortex (DLPFC), insula, (figure 10, in light blue, see Table 3 for a complete report). These regions are typically in effort processing (Krebs et al., 2012; Vassena et al., 2014). In the same contrast, a number of posterior parietal regions were also activated, which are normally involved in attention (Cabeza and Nyberg, 2000; Corbetta and Shulman, 2002) and numerical cognition (Arsalidou and Taylor, 2011). Given that task involved arithmetic operations, this further confirms that increasing task difficulty was associated with more important recruitment of task-relevant regions.

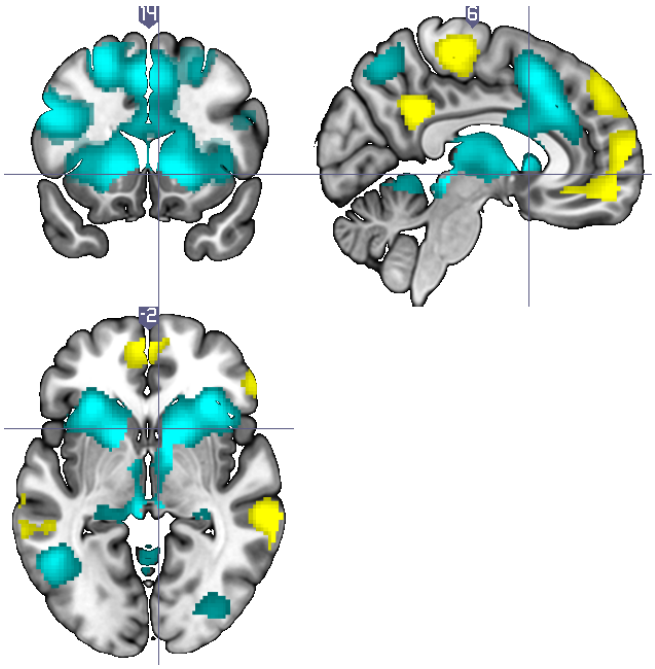

Figure 10: Task-related activation. Parametric effort contrast during task execution in the anticipation of performance phase (light blue). Negative parametric effort contrast during task execution in the anticipation of performance phase (yellow).

Conversely, the negative parametric effort contrast highlighted regions that were more active for lower effort levels (Figure 10, in yellow). This contrast revealed a number of medial frontal and posterior regions, consistently reported as being part of the Default Mode Network (DMN, Raichle et al., 2001, see Table 3 for a complete report), among which ventromedial Prefrontal Cortex (vmPFC), medial Superior Frontal Gyrus (SFG) posterior Insula, Posterior Cingulate cortex (PCC). Middle temporal activation and lateral posterior parietal activation were also reported in this contrast, also consistent with the DMN.

Table 3: Summary of the activation results during task execution

Area	*MNI Coordinates x y z*	*cluster-level FWE*	*cluster-level FDR*	*cluster size*	*peak T*
Parametric contrast for effort during task execution					
Middle frontal gyrus	-24 4 56	0.000	0.000	21151	11.93
Inferior frontal gyrus	-44 6 28				10.5
Precuneus	-10 -68 50	0.000	0.000	9466	10.67
	-26 -70 34				10.44
Superior parietal lobule	-26 -66 44				9.92
Middle temporal gyrus	-50 -56 -4	0.030	0.015	309	8.39
Superior frontal gyrus	38 40 38	0.004	0.002	519	6.22
Inferior frontal gyrus	48 6 28	0.056	0.020	253	5.24
Occipital cortex	38 -82 -4	0.036	0.015	291	4.51
	30 -90 0				4.39
Negative parametric contrast for effort during task execution					
Angular gyrus	52 -64 38	0.000	0.000	2975	7.38
Inferior parietal lobule	54 -58 46				6.58
Inferior Temporal Gyrus	60 -16 -20				5.9
Inferior frontal gyrus	-50 36 -14	0.079	0.041	223	6.38
	50 38 -16	0.012	0.008	392	6.34
Angular gyrus	-54 -62 38	0.000	0.000	2844	6.05
	-48 -68 44				5.79
Superior temporal gyrus	-58 -64 16				5.33
Posterior Cingulate	4 -46 32	0.001	0.000	738	5.85
Paracentral Lobule	8 -26 64	0.000	0.000	1067	5.38
	-12 -34 68				3.61
Posterior Cingulate	0 -24 42				3.33
Superior frontal gyrus	14 50 44	0	0.000	2740	5.29
Middle frontal gyrus	2 30 -16				4.93
Superior frontal gyrus	10 62 10				4.89
Posterior insula	36 -14 18	0,102	0.048	202	4.31
Rolandic operculum	52 -6 8	0,029	0.017	310	3.93
Supramarginal gyrus	58 -22 22				3.85
	46 -30 26				3.50

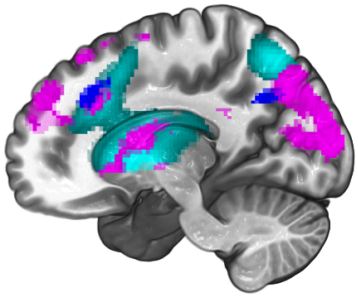

Figure 11: Activation overlap of the parametric effort contrasts during decision making (blue), anticipation of performance (violet) and task execution (light blue).

Interestingly, activity during task execution partially overlapped in the ACC with activity during decision-making and anticipation of performance (Figure 11).

Individual differences analysis

Across participants, choice behavior during the decision-making phase showed considerable variability (see Behavioral Results section). Therefore, one further correlation analysis was performed to investigate inter-individual differences in effort encoding during decision-making. Interestingly, the regression coefficient of the parametric effort contrast in the ACC ROI was correlated across subjects to acceptance rate of the cue ($r=.57$, $p=.005$, Figure 3d). Higher intensity for the parametric contrast reflects a steeper linear increase in the response of this region as a function of increasing effort. This might be interpreted as more efficient encoding across different effort levels (effort encoding). In this case, this higher intensity was associated with increased likelihood of choosing to engage in the more effortful task. Interestingly, effort encoding in ACC was not correlated to

choice entropy (r=.006 , p=.98), thus excluding this potential confound. This is also confirmed when both entropy (beta=.06, p=.771) and acceptance rate (beta=5.82, p=.006) are introduced as predictors of effort encoding in the same linear regression model.

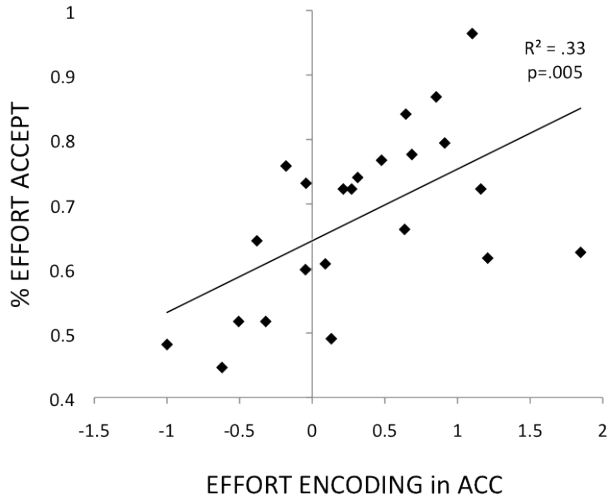

Figure 12: Effort encoding in the ACC during decision making (effort parametric contrast, x-axis), plotted as a function of effort acceptance rate (%, y-axis).

DISCUSSION

Despite the growing interest in the topic, the neural mechanisms underlying effort-related decision making and effort exertion remain debated. In the current study, we dissociated effort-related decision making and anticipation of effortful performance, to investigate effort encoding in both situations. We tested divergent predictions of net-value account and motivational account of ACC function. We show that effort is encoded by the ACC in a motivational fashion, and that this holds across decision-making and anticipation phases. Furthermore, effort encoding generally follows a parametric trend, although it is modulated by phase. The relevance of the current results in the light of the literature is discussed below.

In the decision-making phase, no evidence for a net-value encoding was reported. Higher effort expectation was associated with increased activation in the ACC and the Precuneus (see figure 7a). A few studies showed an ACC contribution to effort-related decision making (Prévost et al., 2010; Kurniawan et al., 2013; Schouppe et al., 2014), and our results confirm this pivotal role. Moreover, we show that ACC encodes effort parametrically, and in a motivational fashion. Precuneus activation is reported in a number of studies across different domains, and seems to be involved in default mode network (DMN) activity (Raichle et al., 2001) as well as in a variety of tasks (Cavanna and Trimble, 2006). The potential contribution of this region to decision-making certainly deserves to be investigated in depth in further research. Reward-related activation during the decision-making phase was also addressed (high reward > low reward), identifying mainly extrastriate areas. Surprisingly, no significant activation was reported in the typical reward-related areas. This might depend on

power or saliency, given that only two reward levels were presented, as opposed to four effort levels. It is however clear that the reward manipulation was effective, as it affected choice behavior (see Behavioral Result section). It should be noted that visual activation is often reported in reward contrasts (high reward > low reward) (Krebs et al., 2012) , especially when visual cues are used. One possible explanation is the increased learned relevance of the cue itself, but this should be addressed in further research.

In the performance phase (Figure 7b), a widespread fronto-parietal network was activated, as well as sub-cortical regions. The essential contribution of ACC and striatum in anticipating cognitive effort confirms the results of our previous study (Vassena et al., 2014). Importantly, also in this phase ACC encodes effort in a motivational fashion, showing linearly increasing activation as a function of effort level. The current results provide no support for a net-value encoding. Anticipation of effort in the performance phase also involved a wide fronto-parietal network. Increased activity was detected in DLPFC, SMA, AG and IPL. Activity in the DLPF and SMA is typically associated with the execution of complex tasks (Kong et al., 2005; Sohn et al., 2007). Activity in the AG and IPL is consistently reported in tasks involving numerical cognition (Arsalidou and Taylor, 2011).Given the arithmetic nature of the task, it seems plausible that neural activation in this phase would reflect task-preparation, and more specifically the recruitment of task-relevant resources recruitment and preparation. In this phase, reward-related activation (high reward > low reward) was located in the cuneus, extrastriate cortex, precentral gyrus and SPL. As in the decision-making phase, no typical reward activation was detected. It should be noted that one study on effort describes a similar pattern, where influence of reward is reported during the feedback, but not during the anticipation

phase (Kurniawan et al., 2013). Again, this issue should be further investigated, to identify potential reasons of this variability.

Subsequently, overlap in effort encoding between substrates involved in decision-making and performance was tested in the conjunction analysis. Both choosing to engage in an effortful task and preparing to overcome such effort elicited overlapping activation in the ACC (figure 7c). Moreover, in both conditions ACC shows a motivational-related encoding, with higher activation as a function of increasing task difficulty. This confirms what suggested by previous reports (Krebs et al., 2012; Vassena et al., 2014) and excludes a pure net-value encoding. Interestingly, while preparing for a more effortful task in the performance phase, ACC showed parametric encoding of effort, with linearly increasing activation across the different effort levels. This highlights the crucial role of ACC in accurate estimation of required task engagement, necessary for adequate resource mobilization (Gendolla and Brinkmann, 2005; Sterling, 2012).

Strikingly, decision-making seems to modulate effort encoding, revealing a partially divergent pattern. The targeted ROI analysis revealed that when expecting a low reward, effort encoding was better explained by a quadratic (inverted-U) trend instead, as ACC activity only increased up to effort level 3, then dropping for the highest effort level (see figure 9). ACC has been shown to play a crucial role in supporting task engagement across a number of effort manipulations (Luks et al., 2002; Sohn et al., 2007; Krebs et al., 2012; Vassena et al., 2014). One recent fMRI study reported increased activation in the striatum when participant voluntarily chose the option entailing more cognitive effort, in a paradigm where no reward was delivered (Schouppe et al., 2014). These authors also report a similar pattern for the ACC, although only marginally significant. In other words, ACC

might also be driving effort engagement, when a voluntary choice is required. In the current results, this would be reflected by the quadratic trend, thus encoding effort that the participants are willing to exert. Potentially convergent evidence comes from the behavioral results, showing that (across subjects) increased effort encoding in the ACC predicts higher likelihood of engaging in the effortful task (i.e. higher acceptance rate of the effortful cue, figure 12). This role of prompting engagement and sustaining effortful behavior seems consistent with recent evidence showing that electrical stimulation of the ACC causes autonomical arousal, associated with what the authors call "will to persevere", that is a subjective feeling of increased motivational drive when dealing with a difficult situation (Parvizi et al., 2013).

Taken together, these results might be interpreted as evidence for a recent account of ACC function formulated by Shenhav et al. (Shenhav et al., 2013). These authors propose a new theoretical framework, where ACC would compute the "expected value of control", that is the value of engaging in a certain behavior. Consistent with earlier computational work, ACC computes value (Alexander & Brown, 2011, Silvetti et al. 2011), but not the value of external stimuli. Instead, it would encode the value of a more abstract quantity, in particular, exerting a certain amount of cognitive effort. Hence, the theory combines elements of the two earlier frameworks, as ACC is proposed to calculate the net-value of motivation. In the current task, this would be implemented as the worth of exerting a certain amount of effort, given the potential reward associated to it. This would imply that reward and effort are integrated in the ACC, which determines if undertaking a certain degree of effort is valuable and hence prompts the appropriate response.

One could argue a number of possible alternative explanations for ACC involvement in both stages of the task, besides the net-value account. Concerning the decision-making phase, increased ACC activation has been associated to conflict monitoring (Botvinick et al., 2004). In this perspective, the quadratic trend in the low reward condition might reflect choice conflict. In our case however, there was no significant difference in choice entropy across low reward condition. Moreover, the activation pattern does not even qualitatively follow that predicted by choice entropy values. Another potential interpretation could be a simulation account. While anticipating a certain effort, the mechanisms underlying task execution might be pre-activated in order to facilitate task performance . Similarly, while choosing between different effort levels, one might simulate the offered alternative to make a decision. This explanation might hold for the performance phase, but is not congruent with the activation pattern detected in the decision-making phase. A purely simulative process would entail an entirely linear coding of effort across the different levels. Lastly, we can also exclude a pure cost coding interpretation, as in the decision-making phase, increasing effort doesn't elicit monotonic increase in the activation.

CONCLUSIONS

The current study shows that during decision-making and anticipation of performance, prospective effort is encoded in a motivational fashion, with overlap in the ACC. During the anticipation of performance, ACC activity linearly increases as a function of effort, while during decision it encodes only the effort that's considered worth engaging in the task, thus driving adaptive choice. Speculatively, probability of success (given the exertion of

a certain amount of effort) might play a role in process. For example, one might expect a drop in ACC activity also in the anticipation phase when the required effort outweighs the subject's capacities, thus prompting disengagement. In this perspective, investigating ACC contribution in a wider varying range of effort levels (up to impossible tasks), and still controlling for decision-making, certainly represent fruitful venue for future research direction.

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CHAPTER 5
VALUE-BASED MODULATION OF EFFORT AND REWARD ANTICIPATION ON THE MOTOR SYSTEM [1]

Human actions are driven by the pursuit of goals, especially when achieving these goals leads to reward. Among other effects of anticipating a reward, a striking observation is that it influences the motor systems, boosting motor excitability for potentially rewarded actions and increasing overall motor readiness. However, attaining a reward mostly requires some effort. Neuroimaging research showed that mental effort requirements are encoded by the same brain regions coding for reward expectation. Moreover, effort and reward prospect seem to be combined in an integrative signal. However, whether mental effort (possibly integrated with reward) influences the motor system directly during task preparation, remains debated. To this end, we implemented a mental effort task, where reward prospect and effort requirements were manipulated. During task preparation, TMS was delivered on the motor cortex and motor-evoked potentials (MEPs) were recorded on the right hand muscles to probe motor excitability. The results show for the first time that both mental effort and reward anticipation influence the readiness of the motor system, in a non-action-specific way. Moreover, effort and reward interacted, providing evidence for an integrative value signal effectively modulating the motor system. Interestingly, this effect was strongly modulated by individual differences in the Need for Cognition trait, underlining a pivotal role of subjective effort experience in value-driven preparation for action.

[1] Vassena E., Cobbaert S., Andres M., Fias W. & Verguts T. (2013). Value-based modulation of effort and reward anticipation on the motor system. Manuscript in preparation

INTRODUCTION

Humans are immersed in complex environments and are constantly confronted with behavioral options to choose among, each entailing potential benefits and related costs with respect to achieving goals. Identifying actions which can lead to a desirable outcome, such as reward, is a core skill in adaptive behavior. The benefit associated with a goal is termed value, and encompasses intrinsic value (primary reinforcers like food and sex, Berridge, Robinson, & Aldridge, 2010), as well as learned value (secondary reinforcers like money). A wealth of findings demonstrated that human behavior is strongly driven by value (Kahneman & Tversky, 1979; Trepel, Fox, & Poldrack, 2005). At the behavioral level, this is evident when people need to select a preferred action or stimulus over an alternative. At the neural level, value is encoded by a specific network in the brain, involving subcortical dopaminergic nuclei, the striatum, and the Anterior Cingulate Cortex (ACC, Haber & Knutson, 2010; Knutson & Cooper, 2005; Liu, Hairston, Schrier, & Fan, 2011; Vassena, Krebs, Silvetti, Fias, & Verguts, 2014; Vassena, Silvetti, et al., 2014).

How value drives decision making and subsequent action selection remains an open question. According to recent theories, value influences the motor system during action selection. Motor programs are selected through a competitive process, through which cognitive variables (such as the prospect of a reward) can contribute to determining the winning action plan (Cisek & Kalaska, 2010). This influence might be mediated via top-down modulation of the cortico-subcortical network underlying value estimation on the

primary motor cortex (M1,Hare, Schultz, Camerer, O'Doherty, & Rangel, 2011) .

A direct effect of value computations on the motor system is plausible from an anatomical point of view. The ACC and striatum are part of the limbic loop which forms the interface between emotion and action (Alexander, DeLong, & Strick, 1986; Haber, Kim, Mailly, & Calzavara, 2006), thereby possibly relating value to action. The neurocircuitry of ACC itself has been proposed as being ideally suited for this function (Paus, 2001), given that this region is part of both the limbic loop and the motor loop. Furthermore, ACC might affect the motor cortex (M1) via an indirect pathway through the Ventral Tegmental Area (VTA). Finally, ACC might modulate the final motor output via projections directly innervating the motor neurons in the spinal cord. These circuits provide an effective pathway for a modulation of value computation on action preparation. A first functional evidence of this network effectively mediating value translation to M1 is provided by a connectivity study. Hare and colleagues (2011) showed increased functional coupling between ventromedial Prefrontal Cortex, encoding stimulus value (Hare, Camerer, & Rangel, 2009; Liu et al., 2011; Vassena, Krebs, et al., 2014), dorsomedial Prefrontal Cortex (dmPFC, of which ACC is a part) and Intra-Parietal Sulcus (IPS). The authors hypothesize dmPFC and IPS to deal with the comparison between available options. Crucially, dmPFC and IPS also showed increased functional coupling with M1 at the time of decision.

An ideal technique to test this hypothesis directly is Transcranial Magnetic Stimulation (TMS). Delivering TMS pulses to M1 and simultaneously recording motor-evoked potentials (MEPs) on hand muscles allows to measure cortico-spinal excitability (CSE). Hence, by looking at the

modulatory effect of value manipulations on CSE, we can have a direct measure of the influence of value on the primary motor system.

Two recent studies used this method to investigate the hypothesis that value influences action selection. Klein-Flugge and Bestmann (2012) showed that the increase in CSE due to TMS prior to choice correlated with the value attributed to the chosen option based on reward magnitude and reward probability. Klein and colleagues (Klein, Olivier, & Duque, 2012) asked participants to perform left or right key presses depending on a given instruction. However, the instruction was sometimes ambiguous, in which case either response would be considered correct. The performance was rewarded at every trial, but one hand was implicitly associated to larger reward. As a result, participants biased their choices in the ambiguous condition towards the more rewarded hand. Importantly, more rewarded responses were associated with higher MEPs in the preparation phase. Hence, these two studies reported an value-driven action-specific increase in CSE, thus showing a modulation of cognitive factors on motor selection. Whether value can influence the motor system even before a suitable action plan can be implemented, was however not clarified. This question was addressed by Kapogiannis and colleagues (2008), using paired-pulse TMS to probe intra-cortical inhibition in M1. The task consisted of passive viewing of a spinning slot machine. Paired-pulse TMS consist in the delivery of two subsequent TMS pulses, where the second supra-threshold pulse allows to measure the excitatory or inhibitory effect of the first sub-threshold pulse on CSE. Increased reward expectation was associated with increased paired-pulse inhibition. This effect was amplified in trials preceded by reward delivery. Although different from the single-pulse protocol, this study shows a modulation of value on CSE, in the absence of action. Using a

similar TMS protocol, Thabit and colleagues (2011) reported an influence of reward on CSE. This effect was detected at reward delivery, at a moment where no upcoming action could be selected. Conversely, Gupta and Aron (2011) investigated the effect of reward before action planning. In a first experiment, they confronted participants with pairs of food items, and asked them to choose the food that they wanted to eat at the end of the experiment. Before the session, participants rated how strongly they wanted each food item. MEPs on the hand muscles were recorded while food pictures were presented during the task, with synchronized delivery of single-pulse TMS. Strongly wanted items elicited stronger MEPs when displayed on the screen, prior to participants' choice. Interestingly, the action to be performed to accept or reject the current item was still unknown to the participant at that time. Therefore the modulation of reward on CSE was not action-specific. The authors define this effect as 'spill over' into the motor system of the urge for food, that is the motivational drive to obtain food. In other words, a wanted item seems to induce a generalized increase in CSE, even when no final motor output can be implemented yet. A comparable effect was reported by the same authors in a second experiment, where food items were replaced by money. To sum up, these studies showed a modulation of CSE by reward, irrespective of final motor output.

An outstanding question is, however, how effort is related to this modulatory influence of reward on CSE. Indeed, a crucial aspect of value estimation is the effort needed to obtain the reward. The anticipation of effort requirements is crucial for optimal performance and is encoded at the neural level by the same structures estimating values (Vassena, Silvetti, et al., 2014). A first open question is if effort costs implied in obtaining a reward would modulate CSE as well. A second open question concerns the

combination of reward and effort information in an integrated value signal. Such signal has been reported in ACC and striatum, which seem to respond to the net-value of a stimulus, namely its rewarding value discounted by the cost implied in obtaining, such as an effort requirement (Botvinick, Huffstetler, & McGuire, 2009; Croxson, Walton, O'Reilly, Behrens, & Rushworth, 2009; Kennerley, Dahmubed, Lara, & Wallis, 2009). Therefore, effort and reward prospect might interact in influencing CSE to optimize preparation for action. Also the direction of the effects of effort and reward will be informative. Indeed, besides the net-value account, a motivational account of ACC has been proposed. Expecting to perform a more effortful task is associated with increased ACC and striatal activation, showing overlap with activity during reward anticipation (Krebs, Boehler, Roberts, Song, & Woldorff, 2012; Vassena, Silvetti, et al., 2014). Hence the effect of reward and effort might follow a net-value coding (highest CSE for the highest net-value option, high reward and low effort prospect) or a motivational coding (highest CSE for conditions requiring more engagement, high reward and high effort prospect). The goal of the current study was to address these questions, using single-pulse TMS to measure CSE in a mental effort task, where both potential reward and prospective effort were manipulated. To this end, we adapted a mental effort task from a previous fMRI study (Vassena, Silvetti, et al., 2014) to the timing used by Gupta and Aron (2011).

MATERIALS & METHODS

Participants

Twenty-two healthy subjects participated in this study, with an average age of 25 (range 20-40). All participants were right-handed males, with no history of neurological or psychiatric disorders. The experimental protocol was approved by the ethical committee of the University Hospital of Gent. Each participant signed an informed consent prior to participation.

Experimental procedure

A mental effort task was implemented, adapting a previous version we used in an fMRI experiment investigating anticipation of effort (Vassena, Silvetti, et al., 2014). In this new version, visual stimuli were introduced as cues (Figure 1). Each cue consisted of a grey circle with a superimposed grid. The horizontal lines of the grid represented the level of effort, which could be low (lower line in black) or high (higher line in black). The vertical lines represent the potential reward, which could be low (left line in black) or high (right line in black). These type of cues have been successfully used to convey combined information about effort and reward (Croxson et al., 2009). We opted for a 2 x 2 design, resulting in two possible levels of effort (easy/hard) and two possible levels of reward (low/high). Thus, there were four possible cues, and each cue indicated a combination of a certain effort requirement and a potential reward (low effort/low reward, low effort/high reward, high effort/low reward, high effort high reward). One additional cue was used, where only the gray circle with no black lines was presented. This cue represented the baseline condition. In this condition, a series of letters was presented on the screen, with the same timing of the other conditions.

The participants were told that after the baseline cue they were not supposed to perform any task, and that their final response would not matter.

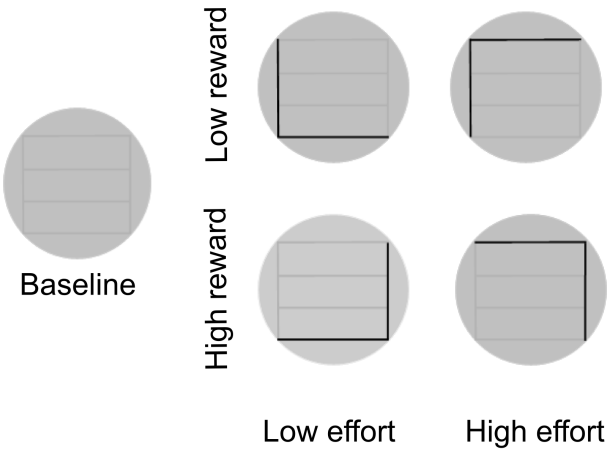

Figure 1: Visual Cues. Five possible cues were presented to the participant. The grey circle with no black lines represents the baseline condition. This cue is followed by the presentation of letters, on which participants don't have to perform any task. Horizontal black lines represent effort level (low/high). Vertical black lines represent reward (low/high). This results in four possible combination: low effort/low reward, low effort/high reward, high effort/low reward, high effort/high reward

Each cue was presented 21 times, thus resulting in 105 trials in total. Every trial consisted of a mental calculation (except for the baseline condition trials). Each calculation was formed by 5 single digit numbers flashing on the screen, thus resulting in 4 subsequent operations (Figure 2). The last digit was followed by a display showing two possible results, one on the left and one on the right. Participants had to select the result they thought to be correct.

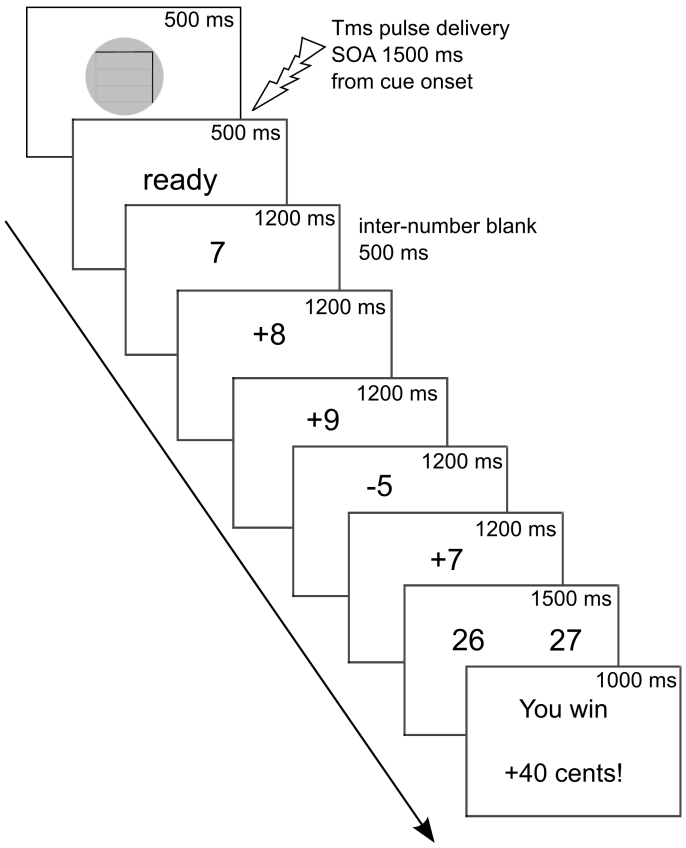

Figure 2: Task structure and timing. Every trial starts with one of the five possible cues. The TMS pulse is delivered with a stimulus onset asynchrony (SOA) of 1500 ms from the cue onset, and 500 ms before the ready display. At the ready display, participants have to press the right key as fast as possible to start the trial, with a maximum response time limit of 500 ms. Subsequently, the digits composing the calculation are presented. Every digit stays on screen for 1200 ms. Every digit is preceded and followed by a blank screen lasting 500 ms. After the last digit, the result display appears on screen, and the participant are supposed to pick the correct result, by pressing the left of the right key. After the key press, they receive feedback (win or lose).

The easy task consisted of calculations with no carrying or borrowing, while in the hard task each operation required carrying of borrowing. This manipulation of mental effort proved effective in our previous study (Vassena, Silvetti, et al., 2014). The low reward was 20 cents and the high reward 40 cents. Participants were instructed to try to be both fast and accurate. The time limit for responding was 1500 ms. In case of late response or wrong response, participants were told that they would lose the same amount of money they were playing for (to be subtracted from their accumulated budget).

Each trial started with one of the five possible cues for 500 ms. Subsequently, the single TMS pulse was delivered (stimulus onset asynchrony from cue 1500 ms). 500 ms after the pulse, a screen appeared displaying the word "READY". Participants were supposed to press the right-hand key as fast as possible, within a limit of 500 ms. After this key press, the task started. If the response to this ready display would be too slow, they were told that the current trial would not be considered for the final calculation of the reward. The timing of the TMS was selected on the basis of Gupta and Aron (2011). In that study, the authors showed that this timing is optimal to elicit a value-related MEP. Also, they showed that this would not be the case in absence of action (experiment 2). For this reason we introduced the response to the ready display to elicit MEPs reliably. Importantly, this action was always the same in every trial and was unrelated to the task. Crucially, the pulse delivery was far apart in time from the final motor response to the calculation result, to avoid the potential confound of interference with the final motor response.

Before administering the task, participants underwent a training phase to familiarize with the task . This phase consisted of a short version of the

task (9 trials), with no TMS applied. Only in this training phase, each trial was followed by two questions, asking subjects to rate difficulty and pleasantness experienced during the trial (scale of 1 to 7).

After the experiment, participants filled in two questionnaires: the BIS/BAS scale, measuring behavioral inhibition and activation (Carver & White, 1994), and the Need for Cognition scale, measuring the tendency to engage in and enjoy thinking (Cacioppo, Petty, & Kao, 1984). The Need for Cognition scale was included because several studies reported an influence of this trait on effort, both in subjective experience and actual task performance (Cacioppo, Petty, Feinstein, & Jarvis, 1996; Coutinho, 2006; Sorrentino, Bobocel, Gitta, & Olson, 1988).

TMS and electromyography

Single pulse TMS was delivered through a biphasic magnetic stimulator (Rapid^2 Magstim, Whitland, UK) connected to a polyeruthane-coated figure-of-eight coil (5.4-cm inner diameter windings). The coil was held tangentially over the left hand motor area, with the handle pointing backwards and forming an angle of 45° with the sagittal plane. Electromyographical (EMG) activity was recorded with the ActiveTwo system (BioSemi, Amsterdam, The Netherlands). Sintered 11x17-mm active Ag–AgCl electrodes were placed over the right First Dorsal Interosseus muscle (FDI) in a belly–tendon arrangement. The FDI contributes to flex or abduct the index away from the middle finger.

The hot spot in the hand motor area was established by locating a stimulation site where TMS elicited reliable motor-evoked potentials (MEP) in the FDI. This position was marked on a closely fitting cap. TMS intensity was set at 110% of the resting motor threshold, i.e. the minimum intensity to

induce an MEP ≥ 50 μV peak to peak in more than 4 out of 10 trials. The average intensity (± S.D.) was 65.2 ± 8.11 % of the maximal stimulator output. EMG signal was amplified (internal gain scaling), digitized at 2 kHz, high-pass filtered at 3 Hz, and stored on a PC for off-line analysis. The peak-to-peak amplitude of the MEPs was computed using Matlab. In order to control for noise and fluctuations in the signal, EMG data were trimmed according to three criteria. Trials were excluded when the root mean square of the background EMG signal recorded 500 ms before TMS was higher than 50 mV (1,45%).Trials where the MEP amplitude was below 50 μV (3,47%) were removed. Trials with MEP amplitude more than 3 standard deviations above or below the individual mean (1,35%) were also excluded.

Data analysis

First, the behavioral data from the training phase were analyzed. A repeated-measures ANOVA was performed on the difficulty ratings with effort (low/high) and reward (low/high) as factors. A second repeated-measures ANOVA was performed on the pleasantness ratings, with effort (low/high) and reward (low/high) as factors. The goal of this analysis was to test if high effort trials were actually perceived as more difficult, and if this was perceived as unpleasant (Kool, McGuire, Rosen, & Botvinick, 2010).

Subsequently, behavioral data from the task were analyzed. Two repeated-measures ANOVA were performed, with accuracy on the calculation task and reaction times as dependent variables. In both models, the factors were effort (low/high) and reward (low/high).

MEP amplitudes in the five conditions were computed. For each participant the average MEP associated with the baseline was subtracted from the average MEPs in the four experimental condition. The goal of this procedure was to control for inter-individual variability in MEPs.

Subsequently, a repeated-measures ANOVA was performed on this data, with effort (low/high) and reward (low/high) as factors. Planned comparisons were also performed on the four experimental conditions. Then, a median-split analysis was performed, on the basis of the scores at the Need for Cognition scale (NFC). The goal of this analysis was to explore the influence of individual differences in effort perception on CSE. Participants were split in two groups (low NFC/high NFC). The factor group was introduced in the previous model, resulting in a rANOVA with effort, reward and NFC group as factors. To test for the reliability of possible effects a rANOVA was also fit to each group separately, with effort and reward as factors. Subsequently, planned comparisons were also performed.

RESULTS

Two participants were excluded from further analyses due to technical failure of the equipment during the experiment. Subsequently, two more exclusion criteria were applied to the MEPs data, on the basis of task performance. Trials were excluded when the final response to the calculation was incorrect (14,7 %). The reason for this was that cognitive processes that lead to an error might differ from successfully completed trials, and this was not the target of the current experiment. Finally, trials were excluded where participants did not press the key at the ready display within the time limit (16,4%). The reason for this was that they were told that in such circumstances the current trial would not count anymore and this might interact with MEPs. For one participant, only 33 trials in total survived all our criteria, especially due to slow response time to the READY display. The main analysis was run both with and without this participant, leading to

similar results. The data from this participant were excluded from further analysis anyway, as in all conditions less then 10 trials per condition were left. For the remaining participants, there were on average 14.4 ± 3.35 trials in the low effort/low reward condition, 13.75 ± 3.07 trials in the low effort/high reward condition, 12.8 ± 3.21 trials in the high effort/low reward condition, and 13.4 ± 3.41 trials in the high effort/high reward condition.

Behavioral data

First, the rating data from the training phase were analyzed. Participants perceived high effort trials as more difficult (main effect of effort $F_{(1,18)}$=22.92, p<.001, η_p^2 =.56), confirming the effectiveness of the manipulation. No significant effect of reward on perceived difficulty ($F_{(1,18)}$=3.24, p=.089, η_p^2 =.15), nor effort x reward interaction were obtained ($F_{(1,18)}$=1.29, p=.27, η_p^2 =.07). The pleasantness ratings did not show any significant effect (main effect of effort $F_{(1,18)}$=1.455, p=.24, η_p^2 =.08, main effect of reward $F_{(1,18)}$=3.17, p=.092, η_p^2 =.15, effort x reward interaction $F_{(1,18)}$=1.12, p=.30, η_p^2 =.06).

Second, the behavioral data from the task were analyzed. The accuracy in the calculation task was 81.2 % (±7%). The repeated-measures ANOVA showed a main effect of effort ($F_{(1,18)}$ =8.57, p=.009, η_p^2 =.32, and no effect of reward ($F_{(1, 18)}$=.199, p=.66, η_p^2 =.01) nor effort by reward interaction ($F_{(1,18)}$=.36, p= .56, η_p^2 =.02, see Figure 3). Pairwise comparisons showed a significant difference between low effort/low reward and high effort/low reward conditions ($t_{(18)}$ = 2.247, p = 037, d=.52), and between low effort/high reward and high effort/low reward conditions ($t_{(18)}$=2.786, p=.012, d=.64). Hence, the effect of effort on accuracy confirmed that the

effort manipulation was successful, as performance worsened in the high effort condition.

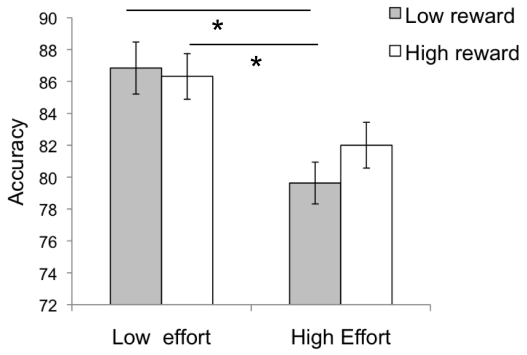

Figure 3: Accuracy results. The plot reports the average accuracy in each of the four experimental conditions (% of correct responses). The bars represent one standard error of the mean.

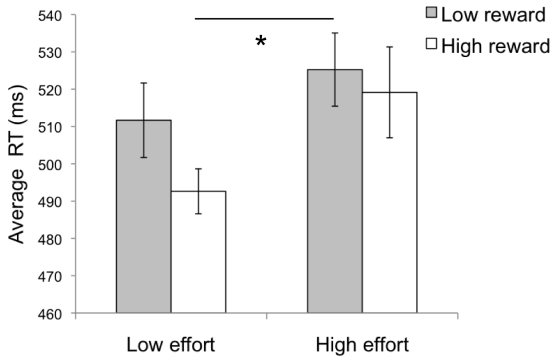

Figure 4: Reaction times. The plot shows average reaction times (RT) in milliseconds in the four experimental conditions. The bars represent one standard error of the mean.

No significant effect was reported in the reaction times (main effect of effort, $F_{(1,18)}$=2.42, p=.14, η_p^2 =.12, main effect of reward, $F_{(1,18)}$= 2.31, p =.15, η_p^2 =.11, effort x reward interaction, $F_{(1,18)}$ =.297, p=.59, η_p^2 =.02, see Figure 4). The absence of effect on RTs could be attributed to the short response time limit, making the effect of effort evident in the accuracy data.

TMS-MEP data

Subsequently, the MEPs data were analyzed. This analysis showed a significant effort x reward interaction ($F_{(1,18)}$=6.63, p=.019, η_p^2= .27, see Figure 5). No main effect of effort ($F_{(1,18)}$=1.988, p=.18, η_p^2= .099) or reward ($F_{(1,18)}$=.575, p=.46, η_p^2= .03) was reported.

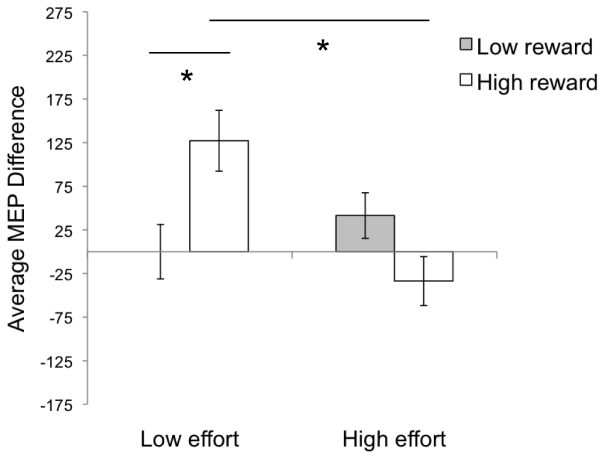

Figure 5: MEP data. The plot shows the average difference in MEP signal (mv) in the four experimental conditions with the respect to the baseline condition. The bars represent one standard error of the mean.

Planned comparisons showed a significant difference between the low effort/low reward condition and the low effort/high reward condition

($t_{(18)}$ = -2.40, p= .027, d=-.55); and between the low effort/high reward condition and the high effort/high reward condition ($t_{(18)}$ = 2.29, p = .034, d=.52). The difference between the low effort, high reward condition and the high effort/low reward condition was not significant, albeit showing a weak trend ($t_{(18)}$ = 1.55, *p* = .139, d=.35).

The median-split individual difference analysis showed an effect of NFC on CSE. When group (NFC low or high) was added to the model, the effort x reward interaction was preserved ($F_{(1,17)}$=6.25, p=.023, η_p^2=.27), but importantly, the interaction effort x group was also significant ($F_{(1,17)}$=17.8, p=.001, η_p^2=.51). When the rANOVA was fit for each group separately, the low NFC group showed a main effect of effort (increased CSE for high vs. low effort, $F_{(1,8)}$=6.26, p=.037, η_p^2=.44), a trend for the interaction ($F_{(1,8)}$=3.58, p=.095, η_p^2=.31), and no effect of reward ($F_{(1,8)}$=1.25, p=.295, η_p^2=.14, see Figure 6).

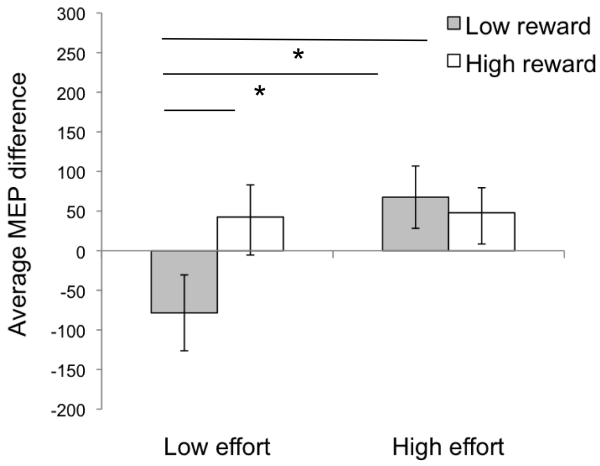

Figure 6: MEP data in the low Need for Cognition group. The plot shows the average difference in MEP signal (mv) in the four experimental condition with the respect to the baseline condition. The bars represent one standard error of the mean.

Planned comparisons showed a significant difference between low effort/low reward and low effort/high reward conditions ($t_{(8)}$=-2.49, p=.037, d=-.83), low effort/low reward and high effort/high reward ($t_{(8)}$=-2.70, p=.027, d=-.90) and a marginally significant difference between low effort/low reward and low effort/high reward ($t_{(8)}$=-2.27, p=.053, d=-.76).

The high NFC group also showed a main effect of effort (increased CSE for low vs high effort, $F_{(1,9)}$=12.7, p=.006, η_p^2=.59, see Figure 6), a trend for the interaction ($F_{(1,9)}$=3.63, p=.089, η_p^2=.29), and no effect of reward ($F_{(1,9)}$=.006, p=.94, η_p^2 =.001). The planned comparisons showed a significance difference between low effort/low reward and high effort/high reward ($T_{(9)}$=2.71, p=.024, d=.86); between low effort/high reward and high effort/low reward ($T_{(9)}$=2.33, p=.045, d=.74); and between low effort/high reward and high effort/high reward ($T_{(9)}$=2.77, p=.022, d=.87).

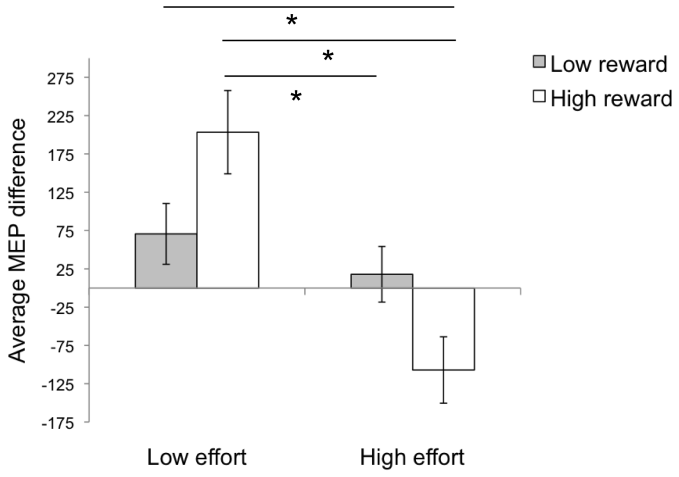

Figure 7: MEP data in the high Need for Cognition group. The plot shows the average difference in MEP signal (mv) in the four experimental condition with the respect to the baseline condition. The bars represent one standard error of the mean.

These analyses show that the main effect of effort is present in both groups but in the opposite direction. People with low NFC show higher CSE when expecting a high effort trial, while people with high NFC show higher CSE when expecting a low effort trial.

DISCUSSION

The current study investigated the influence of anticipating mental effort requirements and reward prospect on motor excitability during task preparation, by measuring CSE while delivering TMS on M1. The goal was to probe sensitivity of CSE to value, when this entails an effort cost. Our results show that both mental effort and reward information can affect the excitability of motor system, even in a non action-specific manner. This evidence suggest that an integrative value signal influences CSE in preparation for action. Moreover, this is modulated by individual differences, potentially suggesting different contributions of neural valuation and motivational system to task preparation.

Traditional theories posited a serial decision process, where first goals are set, the corresponding optimal motor program identified, and finally transmitted to lower level areas to be implemented (e.g., Broadbent, 1958; Sternberg, 1969). The assumption of a motor time separate from decision is explicit in the currently popular diffusion model (Mulder, Wagenmakers, Ratcliff, Boekel, & Forstmann, 2012; Ratcliff & Tuerlinckx, 2002; Ratcliff, 1978). In this process, M1 occupies the lowest level of the hierarchy, merely translating the received programs into action. However, recent accounts reconsidered this functional architecture, postulating that action selection is a parallel and competitive process instead, where multiple action programs are

simultaneously being evaluated, until the winning program is selected (Cisek & Kalaska, 2010). According to these theories, the selection itself happens across all the levels of the hierarchy, and cognitive factors can influence or bias selection also at the level of M1. Supporting evidence for this hypothesis has been provided by a few studies measuring motor excitability via stimulating M1 with TMS and recording MEPs on the hand muscles. These studies showed that CSE can be modulated by a high level cognitive variable such as the value associated to the specific motor program (Klein et al., 2012; Klein-Flügge & Bestmann, 2012). Furthermore, non action specific reward-related modulations of CSE by reward has been reported as well (Gupta & Aron, 2011; Kapogiannis et al., 2008). Taken together, these findings confirm the influence of value and reward information on the motor system. The functional role of this modulation might reside in increasing readiness when possible actions to be performed carry an incentive value, such as leading to a reward (Gupta & Aron, 2011). Reward prospect is indeed known to boost motivation for task performance at both behavioral and neural level (Bijleveld, Custers, & Aarts, 2009; Pessiglione et al., 2007; Vassena, Silvetti, et al., 2014).

Another key factor is the effort entailed in completing a task. The anticipation of an effortful task is associated with increased neural activation of cortico-limbic regions. This activation overlaps in the striatum and ACC with activation induced by a prospect of a reward (Krebs et al., 2012; Vassena, Silvetti, et al., 2014). These regions are also notably implicated in value-based decision making (Rangel & Hare, 2010; Rushworth, Noonan, Boorman, Walton, & Behrens, 2011; Vassena, Krebs, et al., 2014). In fact, evidence suggests that both effort and reward information is combined in the ACC in an integrative signal termed net-value (Croxson et al., 2009;

Kennerley et al., 2009). In the framework of competitive action selection theories, this leads to the prediction that anticipating effort might influence motor excitability as the anticipation of a reward does (Gupta & Aron, 2011). Our results provide the first confirming evidence for this prediction, showing that motor excitability is modulated by both reward prospect and effort requirements. This emerges from the interaction effect, driven by increased motor excitability in the low effort/high reward condition, as compared to the high effort/high reward condition. This suggests that both effort and reward are evaluated, and presumably integrated in a combined signal, which then modulates motor excitability. This computation could be mediated by the ACC and striatum, as suggested by neuroimaging evidence (Botvinick et al., 2009; Croxson et al., 2009; Prévost, Pessiglione, Météreau, Cléry-Melin, & Dreher, 2010). Given the high level cognitive nature of this computation, this result is line with the hypothesis of competitive hypothesis of action selection (Cisek & Kalaska, 2010), confirming that cognitive factors actively bias this process. Previous studies showed this modulation to be action specific, facilitating actions associated with a reward (Klein et al., 2012; Klein-Flügge & Bestman, 2012). Our study shows that value can modulate motor excitability in a non action specific way, presumably increasing readiness for task performance (Gupta & Aron, 2011).

Furthermore, this effect was strikingly moderated by individual differences at the Need for Cognition (NFC) questionnaire. This questionnaire measures a trait which has been defined cognitive motivation (Cacioppo et al., 1984). People with higher NFC tend to engage more in thinking or in cognitively demanding tasks. Besides showing a preference for demanding tasks, this results in higher exposure to mentally demanding situations and in the tendency to actively seek and process more information.

Some studies also report this trait to be correlated with task performance (Coutinho, 2006), low level visual processing (Fleischhauer, Miller, Enge, & Albrecht, 2014), and learning new complex skills (Day, Espejo, Kowollik, Boatman, & McEntire, 2007). Recently, Hill and colleagues (2013) showed that NFC correlates with measures of fluid and crystallized intelligence, but not with working memory capacity. Given the association of this trait with different tendencies in effort-related behavior, we hypothesized that NFC would predict differences in motor excitability prior to task engagement as well. For this reason we split our sample in a low NFC and high NFC group. As predicted, NFC group interacted with effort, thus showing a different effect of anticipating an effortful task on motor excitability as a function of NFC trait (low/high). Strikingly, in both groups the effort x reward interaction was preserved, showing that both group kept both effort and reward prospects into account. However, the effect of effort on CSE in the two groups was opposite. The low NFC group showed increased CSE in the high effort condition (irrespective of reward), and in the low effort/high reward condition (though marginally significant). The high NFC group showed reduced CSE in the high effort condition instead, showing maximal increase in motor excitability in the low effort/high reward condition instead. Sorrentino and colleagues (1988) showed that perception of cognitive effort is modulated by relevance, with people with low NFC reporting more experienced effort in highly relevant conditions. This might be the case in our task, given that at every trial participants can win or lose money. As a result, low NFC people might experience the task as more difficult. Moreover, these people tend to avoid engaging in difficult tasks, and when they do choose to engage, because of the relevance of the task, they might experience greater effort or distress (Cacioppo et al., 1996). Increased CSE prior to high effort trials might reflect a motivational effect, in terms of

readiness in preparation for the task. More precisely, they might rely on anticipatory compensatory mechanisms to increase their chance of completing the task successfully, by preparing more. In fact the similar trend for the low effort/high reward condition is compatible with this interpretation, as previous work demonstrated that both effort and reward can induce motivational effects (Vassena, Silvetti, et al., 2014). A possibly convergent explanation might reside in higher emotional arousal associated with effortful trials. Negative emotional arousal and even worry have been shown to induce increased CSE (Oathes, Bruce, & Nitschke, 2008; van Loon, van den Wildenberg, van Stegeren, Hajcak, & Ridderinkhof, 2010).

Conversely, people with high NFC tend to find effortful tasks simpler, as reported in a mental arithmetic task (Dornic, Ekehammar, & Laaksonen, 1991) and in an anagram solving task (Baugh & Mason, 1986). As a consequence, the high effort condition might not prompt the same motivational CSE increase (in high effort and high reward conditions). In our data however, no difference in accuracy across groups was reported, nor difference in difficulty perception at the ratings during the training. However, the training consisted only of 9 trials, resulting in 2 rating questions per cue. Future studies should foresee more extensive testing of subjective effort perception, to reliably test the relationship between NFC, subjective experience and CSE prior to task engagement. Moreover, it has been reported that people with high NFC generally engage more in difficult cognitive tasks (Cacioppo et al., 1984). This might result in an expertise effect. Being experienced in engaging in difficult tasks, these people might not need increased preparation during the anticipation phase, and as a consequence they might be more sensitive to the net-value information of the upcoming trial. Taken together, these results show that motor excitability is

modulated by effort prospect, and that this modulation is mediated by individual differences in effort-related behavior.

Interestingly, the dichotomy opposing net-value coding to motivational coding that seems to fit the different CSE profiles of people with low vs. high NFC, mimics the debate on ACC function in effort-related behavior. A number of studies in animals and humans indeed suggested that ACC integrates effort and reward prospects in a net-value signal (Croxson et al., 2009; Kennerley et al., 2009). Recent evidence however, showed that the anticipation of higher effort induced increased ACC activation, supporting a motivational role of this region in supporting effortful behavior. ACC might influence motor excitability via cortico-cortical projections, via midbrain projections or via direct synapses on motoneurons in the spinal cord. If ACC is the driver of this CSE effect, one could derive the prediction that previously reported differences in net-value coding as opposed to motivational coding might be due to individual differences in experiencing effort. This interesting prediction should be investigated in further research.

To sum up, our results provide support for the influence of high level cognitive factors on motor excitability in a non action specific manner. We show that both the effort and reward prospect influence the motor system prior to task execution in a cognitive task. This influence is likely to be result of an integration process, which combines both information in a value signal. This signal is strongly modulated by individual differences in NFC, showing that this variable should be kept into account in further studies.

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CHAPTER 6
GENERAL DISCUSSION

This doctoral dissertation investigated the neural coding of reward and effort, and how they are integrated to guide adaptive behavior during both decision making and task preparation. The goal of the present studies was to bridge different theories of value estimation and motivation, to achieve an integrated view on how these computations drive adaptive behavior, and to unravel the underlying neural mechanisms.

Goal-directed behavior encompasses all courses of action attaining a specific achievement, often represented by a reward, (Rangel & Hare, 2010). Engaging in such behavior implies the ability of quantifying the attainable benefit, as well as the likelihood of its occurrence to optimally guide decisions towards the best available options in the environment. The neural implementation of these computations was investigated in **Chapter 2**. More specifically, we tested the contribution of medial Prefrontal Cortex (mPFC) to outcome coding and reward prediction coding, targeting the hypothesis of a functional dissociation between ventromedial Prefrontal Cortex (vmPFC) and Anterior Cingulate Cortex (ACC). Our results show that that vmPFC encodes the outcome, irrespective of probability and decision-making. ACC was sensitive to reward prediction, with the strongest response to unexpected positive outcomes, irrespective of whether a choice was made or not. Given that the experimental design involved risky decision, it was also possible to investigate in the same data the neural basis of inter-individual variability in risk preference. We therefore also addressed this question (in Appendix), showing that decreased activation in the anterior Insula during gambling was

associated with higher risk preference. The underlying mechanism might consist of an altered risk estimation in this area, potentially driving risk taking behaviors in both healthy controls as well as in pathological conditions.

After determining the neural substrate associated with reward prediction, outcome coding and choice, we moved to investigate another crucial dimension implicated in goal-directed behavior, namely motivation for effort. In fact, earning rewards mostly requires exertion of cognitive or physical effort. Investigating how effort information is processed at the neural level is necessary to characterize mechanisms of motivated behavior. For these reasons, in **Chapter 3** we manipulated both cognitive effort and potential rewards, controlling for temporal confounds, in order to disentangle the neural correlates of anticipating a higher reward and a higher effort requirement. Strikingly, we showed that during the anticipation phase, the same cortico-subcortical network traditionally associated with reward encoding was activated by both high reward and high effort prospect. This network involved the striatum and the ACC. In fact, influential theories of ACC function associate this area with value processing and reward prediction (Amiez, Joseph, & Procyk, 2006; Kennerley, Dahmubed, Lara, & Wallis, 2009; Rushworth & Behrens, 2008; Silvetti, Alexander, Verguts, & Brown, 2013). However this view is incompatible with the evidence that higher effort requirements equally recruit the ACC. The overlap with reward-related activation suggests a motivational nature of this activity, necessary in sustaining effortful behavior, as in overcoming a cost to obtain the reward at stake. This interesting hypothesis is in line with several more recent accounts of ACC functions (Holroyd & Yeung, 2012; Sterling, 2012; Weston, 2012). Moreover, exploratory analyses on our data suggested the

possible involvement of brainstem neuromodutalory nuclei in this mechanism. To sum up, the results of **Chapter 3** challenge the notion of ACC as solely dedicated to value computation. In fact, this controversy is traceable across different research lines and literatures. Single-unit recordings in animals, flanked by neuroimaging evidence in humans and computational work supports the net-value perspective, according to which ACC directly encodes rewards discounted by the costs (Croxson, Walton, O'Reilly, Behrens, & Rushworth, 2009; Kennerley, Dahmubed, Lara, & Wallis, 2009; Silvetti et al., 2011). Lesion studies in animals, neuropsychological evidence and recent neuroimaging studies in humans (including our result) support the motivational perspective instead, according to which ACC activity supports motivated behavior towards a goal, thus showing increased activation when effort requirements become higher (Devinsky, Morrell, & Vogt, 1995; Holroyd & Yeung, 2012a; Krebs, Boehler, Roberts, Song, & Woldorff, 2012; Németh, Hegedüs, & Molnár, 1988; Walton et al., 2009).

In **Chapter 4** we directly investigated this dichotomy (net-value account vs. motivational account) with the goal of determining the nature of ACC contribution to reward and effort anticipation, both during effort-related decision making and during effort anticipation. In fact, despite the pivotal role of ACC in decision making (Brass & Haggard, 2007; Holroyd & Coles, 2008), several studies investigating neural coding of effort did not control for it, testing either choice or anticipation (Croxson et al., 2009; Krebs et al., 2012; Kurniawan, Guitart-Masip, Dayan, & Dolan, 2013; Schmidt, Lebreton, Cléry-Melin, Daunizeau, & Pessiglione, 2012). Given the contribution of this area to both decision-making and effort anticipation phases, combining and controlling for both phases in the same experimental

setting was necessary to better characterize this area's function. For this reason, we implemented an fMRI paradigm where effort encoding was investigated both during decision and during anticipation of performance. Moreover, cognitive effort was manipulated parametrically, to test the hypothesis of linear effort encoding in the ACC. The results showed that during both decision and anticipation, prospective effort is encoded parametrically and in a motivational fashion, with overlap in the ACC. These data support the motivational account of ACC function, as higher effort was associated with increased ACC activity across both phases. Strikingly, effort coding was also modulated by phase. During anticipation of performance ACC showed linear increase. During the decision making phase however, a finer-grained analysis revealed the same linear trend only in the high reward condition, and a quadratic trend in the low reward condition instead. In the low reward condition, ACC activity increased only up to a certain effort level, then dropping for the highest effort possible. This result shows that during effort-related decision making, ACC might encode exclusively the effort one considers worth engaging. Converging evidence comes from individual differences in choice behavior. Participants who chose to endure more effortful trials also showed increased effort encoding in ACC during decision. This evidence is compatible with a recent account of ACC function, postulating the role of this region in encoding the value of exerting cognitive effort, to drive adaptive decision (Shenhav, Botvinick, & Cohen, 2013).

After investigating the neural correlates of value, in terms of effort and reward coding, with fMRI, in **Chapter 5** we went one step further, questioning how these computations actually drive action. To investigate how value influences the motor system during task preparation, we used

TMS to stimulate M1, while recording MEPs on the hand muscles. With this method, a value modulation of motor cortico-spinal excitability had been reported in a few recent studies, showing how reward can both facilitate specific actions and increase overall motor readiness (Gupta & Aron, 2011; Klein, Olivier, & Duque, 2012; Klein-Flügge & Bestmann, 2012). Following from these results, we investigated the hypothesis that anticipating cognitive effort would modulate motor excitability as well, possibly in combination with reward. Moreover, we examined individual differences in effort perception measuring the Need for Cognition (NFC) trait (Cacioppo, Petty, & Kao, 1984), and the influence on motor preparation. Our results show that both anticipation of cognitive effort and reward affects motor excitability in a combined fashion. This suggests that value signals computed in cortical and subcortical areas modulate M1 to bias motor preparation, providing compelling evidence for recent theories of action selection (Cisek & Kalaska, 2010). This effect was strikingly modulated by NFC, with both low and high NFC groups displaying an effect of effort, but in opposite directions. The low NFC group showed a motivational-like pattern, with increased motor excitability for high effort conditions and a trend for high reward. The high NFC showed a net-value-like pattern, with maximal motor excitability for the best value option, namely high reward/low effort. This confirms that high level cognitive factors, such as reward, cognitive effort, and even differences in a personality trait like NFC can affect the motor system modulating motor readiness. Moreover, it is a clear indication that further research on effort-related goal-directed behavior should incorporate finer-grained measures of inter-individual differences, as these determine substantial variability even in low-level processes like motor preparation.

Beyond net-value: a model of adaptive effort allocation

In the empirical chapters, we sought to disentangle the contribution of cortico-limbic structures, with particular emphasis on the ACC, to reward coding, effort coding, decision-making and finally motor preparation. Along this path, we faced the inconsistency of our effort data with the dominating view of the net-value account. **In Chapter 3** we showed that anticipating higher effort was associated with increased ACC activity. This led to further investigate this issue, showing in **Chapter 4** that direct encoding of effort in ACC follows a motivational fashion. In fact, the plausibility of a motivational account of ACC function was also backed up by a series of animal studies (Salamone, Correa, Mingote, & Weber, 2005; Salamone & Correa, 2012) and neuropsychological evidence (Németh et al., 1988). However, thanks to parametric manipulation of mental effort, we were able to identify a different pattern during decision-making in the low reward condition. On the one hand, this quadratic trend suggested that a net-value hypothesis could not be completely falsified, given that a drop in activation for the highest effort level with the prospect of a low reward could be interpreted as a cost-benefit (net-value) computation. On the other hand, the linear coding in the high effort condition, as well as in the anticipation of performance phase, strongly supported the motivational account. Moreover, the results of **Chapter 5** showed that both effort and reward prospect exert an integrative influence on motor excitability. The precise nature of this integration stays however elusive, as the individual differences analysis revealed opposite patterns with respect to effort anticipation, potentially mimicking motivational-like activation (low NFC) and net-value-like activation (high NFC).

These result fostered our theoretical thinking, calling for a framework that could consistently account for all these effects, specifically focusing on the integration of different features in one value signal. Inspired by the empirical results, we adopted a computational modeling approach, aiming at a mechanistic understand of neuro-functional architecture of effort-related behavior, going beyond the net-value versus motivational dichotomy. For the purpose, we employed the reinforcement learning framework (RL, Sutton & Barto, 1998). This framework has been successfully applied in investigating neural mechanisms underlying value prediction. RL models have proven fruitful in simulating ACC function both in reward prediction (Alexander & Brown, 2011; Silvetti et al., 2011), and in motivated goal-directed behavior (Botvinick, Niv, & Barto, 2009; Holroyd & Yeung, 2012b). Hence we decided to frame effort-related behavior as an RL problem as well. More specifically, we consider exerting effort as an action one can choose to perform or not. This action is called *boosting*. The decision of whether to boost or not is driven by the optimization of a utility (value) function, which combines reward and cost. This framing allows to explain how adaptive effort allocation is learned, in a number of different task contexts. Crucially, the same framing can explain how effort is allocated (deciding to boost or not) after all information concerning reward and cost has been learned, and only the adaptive choice of exerting effort or not needs to be made.

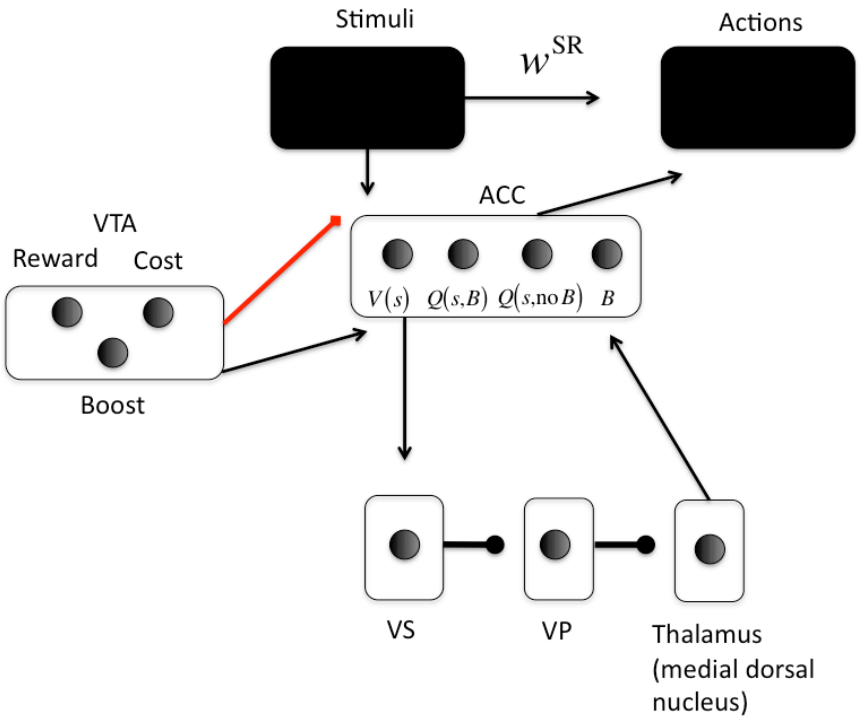

Figure 1: Neurobiological model of adaptive allocation of effort (adapted from Verguts et al., submitted).

Importantly, the model has a modular structure. The black boxes in Figure 1 represent stimulus-response mappings, which have to be learned in a certain task context. This can be mediated via changes in parameters (e.g., neural network weights) w and is independent from the modules that implement adaptive learning of when to boost (white boxes in Figure 1). Potentially any task can instantiate these black boxes, from choosing to press a lever (like in a typical rodent experiment), to performing mental arithmetic. The white boxes represent the machinery that allows the model to learn when to boost or not. The units in the ACC represent the value of a certain

stimulus *s* (*V*(*s*)), the value of boosting given a certain stimulus *Q(s,B*), and the value of not boosting given a certain stimulus Q*(s,noB)*. The value of boosting is thus learned by the ACC per every stimulus. This signal is passed on via ventral striatum (VS), ventral pallidum (VP) and thalamus back to the ACC, where it activates the boosting unit B. When choosing to boost, the B unit will increase the signal-to-noise ratio in the response layer, increasing likelihood of a correct response. Note that the correct task-relevant stimulus-response mapping is learned independently, and that ACC learns when boosting is adaptive, via maximization of its own utility function. In practice, this means that the model learns when it's worth boosting, that is when exerting effort increases the likelihood of selecting the correct response, and thereby the likelihood of reward.

With this architecture, the model manages to simulate several experimental findings. The model simulates the choice behavior of rats in a T-maze setting, when one arm of the maze offers more food, but only after climbing a barrier (Salamone, Cousins, & Bucher, 1994). The model also learns how to allocate effort adaptively when simulating cognitive tasks involving effort and reward, such as calculations (Vassena et al., 2014) and conflict tasks (Egner, Etkin, Gale, & Hirsch, 2008). Interestingly, one can also bias the behavior of the model towards never boosting or always boosting, thus mimicking dopaminergic lesion or depletion in one case (Salamone et al., 1994), and pharmacological dopaminergic enhancement in the other case (Bardgett, Depenbrock, Downs, Points, & Green, 2009). From the behavioral point of view, both cases result in poor performance, as effort is not allocated adaptively (eg. no boosting when it would be worth, and excessive boosting when it's not needed). The paper reporting this model in

detail is currently submitted for publication (Verguts, Vassena, & Silvetti, submitted).

Besides the explanatory power with respect to existent literature, the model also makes an interesting prediction, yet to be tested. For increasing task difficulty, activation of the boost unit shows an inverted U shaped pattern, dropping when difficulty is too high (Figure 2).

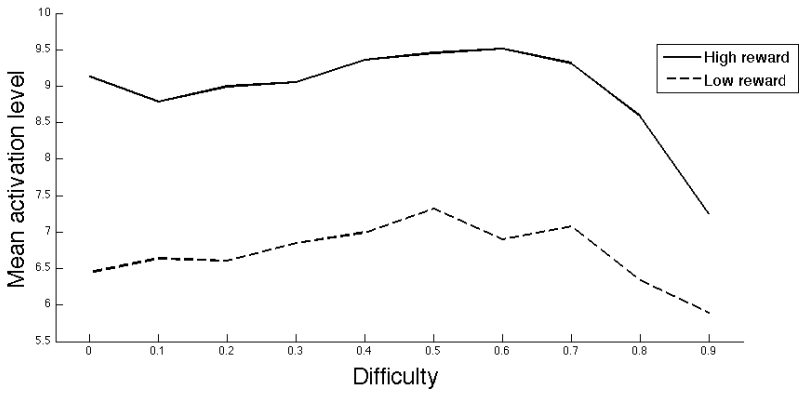

Figure 2: Model simulation. On the y-axis the activity of the boosting unit is plotted. On the x-axis, task difficulty is plotted (adapted from Verguts et al., submitted).

The left part of the curve overlaps with our empirical results of **Chapter 3**, where anticipation of high effort was associated with increased ACC activity. In our study however, accuracy in the task was very high, thus preventing us from sampling from the right side of the curve predicted by model (i.e. higher task difficulty) The results of **Chapter 4** suggest the plausibility of an inverted U shaped pattern, as in the low reward condition during the decision phase, ACC activity drops for the highest effort level. However, in those results ACC activity in the high reward condition is not

consistently higher than in the low reward condition, as opposed to the model. The reason for this discrepancy might reside in the parametric manipulation of effort, which might have decreased saliency of the reward manipulation. This should be investigated in further research.

One first step for further validation of the model, would be to explicitly test the prediction of an inverted U shaped relationship between task difficulty and ACC activity. In fact this prediction is also congruent with the recent theoretical account of ACC function proposed by Shenhav and colleagues (Shenhav et al., 2013). More precisely, the boosting unit in our model influences the decision to allocate effort. In terms of behavior, this should be applicable to both a decision making situation, as well as to an anticipation situation. As a first experiment, one could think of an adapted version of the paradigms we used in **Chapter 4**. Both reward and task difficulty should be manipulated, but this time difficulty should be varied to its extremes, from very easy to very difficult. According to the model, in these circumstances one would predict a drop in ACC activity. As we showed that decision making can modulate effort encoding in the ACC, it would be interesting to test this hypothesis separately in both a decision making and an anticipation context. Following from our empirical results of **Chapter 3** and **Chapter 4**, one might intuitively predict a shift to the right in of the curves in Figure 2 in the absence of choice. Concretely, this corresponds to linear increase in ACC activity, also for higher levels of task difficulty, pushing the activity drop further on the y-axes. In other words, in absence of choice, activity drop would happen for higher difficulty levels as compared to a choice situation. In the absence of choice, choosing to boost represent always the most adaptive behavior, as not doing would imply losing the reward anyway. In a decision-making context however, one would

be allowed for example to opt for a lower effort/lower reward option. To sum up, a possible empirical result would be an inverted-U in both anticipation and decision making, but a right-shifted curve in anticipation. In the model, however, boosting is always implemented as a choice, so finding this predicted result would present yet a further challenge for future model development.

Beyond dopamine: interaction with other neuromodulators

As illustrated in the introduction, reward-related and effort-related neural activation has mostly been associated with regions receiving massive dopaminergic input from the VTA in the brainstem. The results of our fMRI studies confirmed the involvement of the striatum and ACC, dopaminergic targets and part of the so-called reward system (Haber & Knutson, 2010; Knutson & Cooper, 2005). Moreover, pharmacological manipulation or inactivation of dopamine alters effort allocation (Salamone & Correa, 2012).

However, dopamine is not the only neuromodulator known to exert dramatic influence on brain activity and behavior. Noradrenaline (also called norepinephrine), is also known to reach widespread cortical networks. Noradrenaline is spread by the Locus Coeruleus, which is also located in the brainstem. Noradrenaline is generally associated with arousal, and has been proposed to modulate signal-to-noise ratio in neuronal activity in several situations (Aston-Jones & Cohen, 2005), including typical cognitive control tasks (Verguts & Notebaert, 2009). In fact, in our model boosting is also expressed as an increase in signal-to-noise ratio applied on the response layer. Hence, one possible future direction would be to try to combine these frameworks, for example investigating the effect of arousal on effort

exertion, targeting potential noradrenaline-dopamine interactions (Raizada & Poldrack, 2007). A first evidence for these systems interacting in effort-related behavior comes from a recent experiment, where higher arousal induced by pictures influenced physical effort exertions (Schmidt et al., 2009). Including a noradrenergic modulation in the model, might account for these empirical effects.

Serotonin is another major neuromodulator, released by the Dorsal Raphe Nucleus (DRN) in the brainstem, widely reaching cortical and subcortical regions. Classically, serotonin-mediated processes are associated with behavioral inhibition, stress, anxiety and depression (Daw, Kakade, & Dayan, 2002; Graeff, Guimarães, De Andrade, & Deakin, 1996). However, a few theoretical attempts have been made, to elucidate interactions with dopamine (Boureau & Dayan, 2011; Cools, Nakamura, & Daw, 2011; Daw et al., 2002). Complicating these attempts is the fact that serotonergic input to the cortex is far less localized than dopaminergic input (Kranz, Kasper, & Lanzenberger, 2010), thus making it particularly challenging to both measure and modulate with anatomical specificity. Several recent experiments in animals however, seem to provide compelling evidence of a serotonergic contribution to reward processing (Inaba et al., 2013; Izquierdo et al., 2012; Miyazaki, Miyazaki, & Doya, 2012; Nakamura, 2013; Pratt, Schall, & Choi, 2012). Pharmacological manipulation of central serotonin levels in humans also influences reward-related processing and decision making (Cools, Roberts, & Robbins, 2008; Cools, Robinson, & Sahakian, 2008; Homberg, 2012; Schweighofer et al., 2008; Seymour, Daw, Roiser, Dayan, & Dolan, 2012). More specifically, in these studies, altering serotonin levels seems to affect processing of negative events (such as punishments) and costs (delay). This is compatible with our exploratory

analysis in **Chapter 3**, where we show that both high effort and high delay seem to elicit increased brainstem activation in a region compatible with DRN. In line with the reported studies, this might reflect serotonergic activation in response to costs, which need to be overcome to complete the task and achieve the reward. To sum up, extending our model of adaptive allocation of effort by including a serotonergic modulation, might help in elucidating the contribution of serotonin in reward and cost processing.

Serotonin-dopamine interactions: a possible role for the medial Prefrontal Cortex

Further insights in the possible contribution of serotonin are provided by research in clinical settings. Altered serotonin release in the DRN is typically associated with a pattern of behavioral sequelae contributing to the development of depression. This phenomenon is named *learned helplessness*, and implies a number of behavioral depressive symptoms caused by the exposure to uncontrollable stressors (Seligman & Beagley, 1975). Although it is not the sole cause of depression, this phenomenon has been long studied in rodents, mainly to develop animal models with the goal of improving pharmacological treatments (Pryce et al., 2011). The underlying neural mechanism resides in an over-sensitization of DRN serotonergic neurons, which leads to exaggerated serotonergic release, causing the behavioral consequences (Maier & Watkins, 2005). Relevant to our model, is the evidence that the mechanism leading to DRN over-sensitization would be mediated by the mPFC (Amat et al., 2005). This has been confirmed in a more recent study, targeting the underlying mechanisms of mPFC-brainstem interactions while animal where facing a behavioral

challenge (Warden et al., 2012). Crucially, they showed in freely moving rats exposed to stressors, that perseverance in the behavior was associated with mPFC firing. Moreover, optogenetic stimulation of mPFC neurons projecting to the DRN increased this persistence. These results clearly show that mPFC modulates stress-related response in the DRN. This might be especially relevant when investigating adaptive allocation of effort. The mPFC region includes the ACC, which in our model drives effort allocation. According to the predictions of the model, extremely difficult tasks would induce disengagement (inverted U shaped relationship between difficulty and activity of the boosting unit). However, in a situation where disengagement is not an option, continuous (and unavoidable) failure due to excessive task difficulty might parallel the exposure to an uncontrollable stressor. In these circumstances, our model might provide fruitful insights in the cortico-subcortical interaction associated with facing a very difficult tasks, shedding light on mechanisms favoring persistence and resistance to adverse environmental conditions.

Implications for the study of motivation in health and disease

The empirical results, together with the computational work, prompt a theoretical shift in the understanding mPFC function in supporting motivated behavior, merging the net-value perspective with the motivational perspective. The validity of this framework should be broadly put to test, as its explanatory power might account not only for decision-making situations involving effortful behavior. In fact, considering the computational accounts of reward prediction (Alexander & Brown, 2011; Silvetti et al., 2011), it seems plausible that this logic would apply to the factor probability as well.

It would be interesting then to cross effort, reward and probability under this theoretical framework, to test how mPFC processes these factors.

In addition to this, potential clinical implications might derive from this framework. Motivational impairments characterize several psychiatric conditions, including depression, anhedonia, ADHD, and obsessive compulsive disorder (Der-Avakian & Markou, 2012; Devinsky et al., 1995; Milad & Rauch, 2012; Silvetti, Wiersema, Sonuga-Barke, & Verguts, 2013; Treadway & Zald, 2011). Interestingly, these disorders are often associated with alteration or dysfunction of the same cortico-subcortical network reported in our results and implemented in our computational model. Adapting the model to simulate different behavioral and neural activity patterns associated with these disorders might provide new insights in the etiopathogenenetic mechanisms, as well as the development of new pharmacological treatments. Moreover, our empirical results shed new light on the neural mechanisms underlying motivation for effort. Understanding how mPFC (and especially ACC) actively drives engagement and disengagement in motivationally relevant courses of action represents the next challenge. Elucidating these mechanisms will provide us with the key to disclose the actual drivers of motivated behavior. This would open up exciting possibilities of behavioral intervention in people with pathological alteration of motivation, as well as in healthy people facing emotional or cognitive challenges in their life path.

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CHAPTER 7
NEDERLANDSTALIGE SAMENVATTING

Het onderzoek beschreven in dit proefschrift richtte zich op de neurale basis van beloning en inspanning, alsmede de manier waarop deze aspecten betrokken zijn bij het sturen van gepast gedrag tijdens zowel het maken van beslissingen als het voorbereiden op een bepaalde taak. Het doel van de huidige studies was om verschillende theorieën van waarde-inschatting en motivatie bij elkaar te brengen, om zo een integrale visie op de werking van deze aspecten te bekomen en de onderliggende neurale mechanismen te ontdekken.

Doelgericht gedrag omvat alle soorten acties die gericht zijn op een specifiek doel, vaak weergegeven door een beloning (Rangel & Hare, 2010). Het engageren in zulk gedrag geeft aan dat het voor mensen mogelijk is om het te bereiken voordeel te kwantificeren, alsook de waarschijnlijkheid van het plaatsvinden van dit voordeel, zodat er zo optimaal mogelijk afgewogen kan worden wat de best beschikbare opties in de omgeving zijn. De neurale basis van dergelijke afwegingen is onderzocht in **Hoofdstuk 2**. Meer specifiek hebben we de bijdrage onderzocht van de mediale Prefrontale Cortex (mPFC) aan het coderen van uitkomsten en het voorspellen van beloning. Hierbij werd een functionele dissociatie verwacht tussen de ventromediale Prefrontale Cortex (vmPFC) en de Anterior Cingulate Cortex (ACC). Onze resultaten tonen aan dat de vmPFC betrokken was bij het coderen van uitkomsten, ongeacht de waarschijnlijkheid van deze uitkomst en het daadwerkelijk maken van een beslissing. De ACC was betrokken bij het voorspellen van beloning, met name bij onverwachte positieve

uikomsten, ongeacht of er wel of niet een keuze gemaakt werd. Omdat deelnemers gedurende het experiment risicovolle beslissingen moesten nemen, was het mogelijk om tevens de neurale basis van inter-individuele variabiliteit in risico-voorkeuren te onderzoeken. Zoals beschreven in de Appendix toonden de resultaten aan dat verminderde activatie in de anteriore Insula tijdens gokken samenhangt met sterkere voorkeuren voor het nemen van risico. Het onderliggende mechanisme bestaat mogelijk uit een veranderde risico inschatting in dit gebied, wat zou kunnen aansturen op risicovolle gedragingen bij zowel gezonde personen als personen met een pathologische aandoening.

Na het bepalen van het neurale substraat die geasocieerd is met het voorspellen van beloning, het coderen van uitkomsten en het maken van keuzes, onderzochten we in een volgende stap een tweede cruciale dimensie van doelgericht gedrag, namelijk motivatie voor inspanning. Meer bepaald is het zo dat het verkrijgen van beloningen vaak gepaard gaat met het moeten uitoefenen van cognitieve (mentale) of fysieke inspanning. Om te bepalen welke mechanismen ten grondslag liggen aan gemotiveerd gedrag, is het nodig te onderzoeken hoe informatie omtrent inspanning op neuraal niveau verwerkt wordt. In **Hoofdstuk 3** hebben we daarom zowel cognitieve inspanning als mogelijke beloning gemanipuleerd, om de neurale basis van het anticiperen van hogere beloning en een vergrootte inspanning te onderzoeken. Opmerkelijk genoeg demonstreerden de resultaten dat hetzelfde cortico-subcorticale netwerk, dat traditioneel geassocieerd wordt met het encoderen van beloning, ook actief is gedurende de anticipatie fase bij zowel hogere beloning als hogere verwachte inspanning. Dit netwerk omvat het striatum en de ACC. Invloedrijke theorieën omtrent de functie van de ACC associëren het gebied met het verwerken van waarde en voorspellen

van beloning (Amiez, Joseph, & Procyk, 2006; Kennerley, Dahmubed, Lara, & Wallis, 2009; Rushworth & Behrens, 2008; Silvetti, Alexander, Verguts, & Brown, 2013). Deze opvatting is echter niet verenigbaar met recente evidentie die aantoont dat hogere eisen qua inspanning eveneens beroep doen op de ACC. De overlap met beloningsgerelateerde activatie lijkt erop te wijzen dat deze activatie motivationeel van aard is, en noodzakelijk is voor het voortzetten van gedrag dat inspanning vergt alsook het overwinnen van kosten om toch een beloning te kunnen verkrijgen. Deze interessante hypothese sluit aan bij recente ideeën over de functies van de ACC (Holroyd & Yeung, 2012; Sterling, 2012; Weston, 2012). Bovendien wezen enkele exploratieve analyses van onze data erop dat de neuromodulerende cellen in de hersenstam mogelijk betrokken zijn bij dit mechanisme. Samengevat betwisten de resultaten van **Hoofdstuk 3** het idee dat de ACC enkel gericht is op het bepalen van waarde. Deze controverse is terug te zien in verschillende onderzoekslijnen en aanverwante literatuur. Zo wordt de zogeheten *netto-waarde visie*, die stelt dat de ACC beloning rechtstreeks codeert (rekening houdend met de kosten), ondersteund door single-unit opnames bij dieren, evidentie op basis van fMRI studies bij mensen alsook computationele studies (Croxson, Walton, O'Reilly, Behrens, & Rushworth, 2009; Kennerley et al., 2009; Silvetti, Seurinck, & Verguts, 2011). Lesie-studies bij dieren, neuropsychologisch bewijs en recente neuroimaging studies bij mensen (waaronder ook onze resultaten) ondersteunen daarentegen de *motivationele visie*, die stelt dat de ACC gemotiveerd gedrag (in de richting van een doel) aanstuurt, zodat verhoogde activatie zichtbaar is wanneer er meer inspanning noodzakelijk is (Devinsky, Morrell, & Vogt, 1995; Holroyd & Yeung, 2012; Krebs, Boehler, Roberts, Song, & Woldorff, 2012; Németh, Hegedüs, & Molnár, 1988; Walton et al., 2009).

In **Hoofdstuk 4** onderzochten we deze dichotomie (netto-waarde visie vs. motivationele visie) rechtstreeks, met als doel te bepalen hoe en in welke mate ACC bijdraagt tot beloning en het anticiperen van inspanning. Meer specifiek werd dit nagegaan zowel tijdens besluitvorming waarbij inspanning een belangrijke rol speelt, alsook het anticiperen van inspanning zelf. Ondanks de centrale rol die ACC speelt tijdens besluitvorming (Brass & Haggard, 2007; Holroyd & Coles, 2008), werd dit niet gecontrolleerd in studies die neurale codering van inspanning nagaan. Meer bepaald werd enkel keuze getest, ofwel enkel anticipatie (Croxson et al., 2009; Krebs et al., 2012; Kurniawan, Guitart-Masip, Dayan, & Dolan, 2013; Schmidt, Lebreton, Cléry-Melin, Daunizeau, & Pessiglione, 2012). Gezien de bijdrage van dit hersengebied aan zowel besluitvorming als fases van anticipatie van inspanning, was het noodzakelijk om beide concepten te combineren en ervoor te controleren in eenzelfde experimentele proefopzet. Dit had als doel de functie van dit hersengebied beter te onderscheiden en duidelijker af te lijnen. Omwille hiervan implementeerden we een fMRI paradigma waarbij het encoderen van inspanning werd onderzocht, zowel tijdens het maken van een inspanningsgerelateerde beslissing als het anticiperen op een toekomstige inspanning. Verder werd cognitieve inspanning parametrisch gemanipuleerd, om na te gaan of lineaire encodering van inspanning in de ACC plaatsvindt. De resultaten toonden aan dat tijdens zowel besluitvorming als anticipatie, prospectieve inspanning parametrisch geëncodeerd werd en op een motivationele manier, met overlap in de ACC. Deze data ondersteunen de motivationele visie met betrekking tot de functie van ACC, gezien meer inspanning werd geassocieerd met een toename in ACC activiteit overheen beide fases (beslissing en anticipatie). Opmerkelijk, het coderen van inspannng was tevens gemoduleerd door fase. Tijdens het afwachten van een beoordeling van een prestatie vertoonde ACC een

toename op een lineaire manier. Tijdens besluitvorming daarentegen, werd deze lineaire trend enkel gevonden in de hoge beloningsconditie. Er werd een kwadratische trend bekomen in de lage beloningsconditie: Daar nam ACC activatie enkel toe tot een zeker niveau van inspanning werd bereikt, waarbij vervolgens activatie daalde bij het bereiken van maximale inspanning. Dit resultaat suggereert dat tijdens inspanningsgerelateerde besluitvorming, ACC uitsluitend inspanning codeert die men op dat moment de moeite waard vindt. Convergerende evidentie hiervoor komt van individuele verschillen in keuzegedrag. Participanten die ervoor kozen om taken uit te voeren die meer inspanning vergden, toonden ook een toegenomen codering van inspanning in ACC tijdens besluitvorming. Deze bevinding is compatibel met een recente visie omtrent de functie van ACC, die veronderstelt dat dit adaptive besluitvorming ondersteunt door het encoderen van de waarde van het uitoefenen van cognitieve inspanning (Shenhav, Botvinick, & Cohen, 2013).

Na het onderzoeken van de neurale correlaten van waarde, in termen van het encoderen van inspanning en beloning door middel van fMRI, gingen we een stap verder in **Hoofdstuk 5**. In dit hoofdstuk gaan we na hoe deze mechanismes actie aandrijven. Om te onderzoeken hoe waarde een invloed heeft op het motorsysteem tijdens taakvoorbereiding, hebben we gebruik gemaakt van Transcraniale Magnetische Stimulering (TMS) om de motorische cortex (M1) te stimuleren, terwijl gelijktijdig de Motor Evoked Potentials (MEPs) werden geregistreerd op de handspieren. Studies die gebruik maakten van deze methode, hebben reeds een modulering van waarde van motorische cortico-spinale prikkelbaarheid gerapporteerd, die aantoont hoe beloning zowel specifieke acties kan faciliteren als algehele motorische paraatheid kan doen toenemen (Gupta & Aron, 2011; Klein,

Olivier, & Duque, 2012; Klein-Flügge, Hunt, Bach, Dolan, & Behrens, 2011). Volgend op deze resultaten, onderzochten we de hypothese dat anticipatie van cognitieve inspanning motorische prikkelbaarheid ook zou moduleren, mogelijks in combinatie met beloning. We onderzochten daarenboven individuele verschillen met betrekking tot de perceptie van inspanning door middel van de 'Need for Cognition' (NFC) karaktertrek (Cacioppo, Petty, & Kao, 1984), en de invloed op motorische voorbereiding. Onze resultaten tonen aan dat zowel anticipatie van cognitieve inspanning als beloning gecombineerd een invloed hebben op motorische prikkelbaarheid. Dit suggereert dat waarde signalen berekend in corticale en subcorticale gebieden M1 moduleren om motorische voorbereiding te beïnvloeden. Deze bevinding ondersteunt recente theorieën omtrent het selecteren van acties (Cisek & Kalaska, 2010). Dit effect was verrassend genoeg gemoduleerd door NFC, waarbij zowel lage als hoge NFC groepen een effect van inspanning weergaven, zij het in tegenovergestelde richtingen. De lage NFC groep toonde een patroon in de richting van de motivationele visie, met toegenomen motorische prikkelbaarheid voor condities die hoge inspanning vereisen en een trend voor hoge beloning. De hoge NFC groep daarentegen vertoonde een patroon in de richting van de netto-waarde visie, met maximale motorische prikkelbaarheid voor de optie met de beste waarde, namelijk hoge beloning/lage inspanning. Dit bevestigt dat hogere-orde cognitieve factoren, zoals beloning, cognitieve inspanning en zelfs verschillen in persoonlijkheid (NFC) een invloed kunnen hebben op het motorsysteem door motorische paraatheid te moduleren. Verder is het een duidelijke indicatie dat toekomstig onderzoek met betrekking tot inspanningsgerelateerd doelgericht gedrag specifieke metingen van interindividuele verschillen moet incorporeren, aangezien deze een

substantiele variabiliteit meebrengen, zelfs in “lagere-orde” processen zoals motorische voorbereiding.

Tenslotte vatten we in de **Algemene Discussie** de bevindingen samen, en bespreken we implicaties voor toekomstig onderzoek alsook beperkingen. Verder illustreren we een nieuw neuro-computationeel model van adaptieve toewijzing van inspanning, parallel ontwikkeld met ons empirisch onderzoek en deels ervan afgeleid. Dit model verheldert de controverse die bestaat tussen de netto-waarde en motivationele visie met betrekking tot cortico-limbische structuren, door motivatie voor inspanning te implementeren als een adaptieve gedraging, die kan aangeleerd worden via *beloningsleren*. Concluderend bespreken we de implicaties van onze bevindingen voor toekomstig onderzoek, alsook de potentiële relevantie voor klinische doeleinden.

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