Interindividual variability in the dimensions of goal-directed behaviour and their neural correlates.

Inauguraldissertation

zur Erlangung des akadamischen Grades eines Dr. phil. im Fach Psychologie, eingereicht an der Fakultät für Verhaltens- und Empirische Kulturwissenschaften der Ruprecht-Karls-Universität Heidelberg.

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geboren am 22.06.1981 in Luxemburg.

Heidelberg, im Februar 2010

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Tag der Disputation: 15.06.2010

Acknowledgements

First and foremost, I want to thank PD Dr. Stefan Kaiser for his outstanding scientific and moral support throughout this dissertation project. His valuable feedback and omnipresent assistance have allowed me to work in a fulfilling and productive environment. Additionally, I want to thank Stephan Walther for many interesting discussions and for helping me to familiarise myself with the methodological and statistical aspects of functional imaging. I also want to thank Kerstin Herwig for patiently contributing to the organisational success of this work, as well as Prof. Dr. Matthias Weisbrod for providing the necessary framework.

I want to thank Prof. Dr. Christian Fiebach for supporting this project and for his valuable comments. My integration in the research and training program "Goals and Preferences" allowed me to take part in interesting symposia and discussions with diversified topics which were a steady source of inspiration. Accordingly, I want to thank my colleagues Andrea Gäbel, Julia Müller and Carola Barth, as well as the members of the FIMLAB for interesting discussions.

I am deeply thankful for the enormous support during all those years from my parents, Josée and Gregoire, my sister Michelle as well as my partner Anouk. This would not have been possible without their help.

Last, but not least, I want to thank all the participants of the studies who have kindly offered their time and without whom this research could not have been realised.

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1. Introduction

Goal-directed behaviour (GDB) is a fundamental aspect of human interaction with the environment. It governs most activities, whether they are directed towards objects or other people. Dickinson and Balleine (1994) argued that a “directed” action needs to be mediated by knowledge of the contingency between itself and the outcome, as well as the perception of the outcome as a “goal” for the actor. Additionally, the motivation to engage in a specific goal-directed activity relies on the mental representation of the goal itself (Bandura, 1991).

The mechanisms of purposive behaviour are modulated by a vast array of psychological processes. Personality traits, cognitive capabilities, behavioural regulation and psychiatric disorders are just a few examples of crucial factors in the understanding of GDB. They all exert modulatory influences on GDB and therefore account for interindividual differences. We will focus here on two fundamental aspects of GDB, namely sensitivity to rewards as well as inhibition of unwanted responses. Sensitivity to rewards can be characterised as individual differences in appetitive functioning (Gray, 1970). Impulsivity is specified as a type of behaviour which is premature and inappropriate (Daruna & Barnes, 1993).

Besides interindividual differences occurring in the normal, non-pathological range, certain psychiatric disorders have deteriorating effects on the formation of purposive behaviour. Psychological theories about the characteristics of GDB in the general population can be consolidated by models of psychopathology specifying the exact impact of these disorders on GDB. Schizophrenia, a frequent and debilitating condition, is characterised by a number of symptoms closely related to GDB. Three common observed symptoms have a particular importance in this context: apathy, which is conceptualised as a lack of motivation; anhedonia, i.e., the inability to experience pleasure; and depression, an important co-occurring syndrome in schizophrenia.

In order to provide an exact account of the influence of reward sensitivity, impulsivity and schizophrenia on GDB, the neural correlates of these elements need to be taken into account. Functional imaging can inform our understanding of these elements beyond the scope of overt behaviour. Connections between frontal and subcortical regions have been proposed as an important neural correlate of GDB (Mega & Cummings, 1994). For example, the processing of rewarding incentives is thought to be mediated by connections between medial prefrontal and ventral striatal

regions, and dysfunctional activation of this network is seen as an important factor in the etiology of schizophrenia (Weinberger, 2001). Inhibition of prepotent responses is also closely related to a frontal-subcortical network encompassing lateral – prefrontal regions (e.g., Asahi et al., 2004; Horn et al., 2003).

But the exact relation between activity in the specific frontal-subcortical circuits and the aforementioned concepts still remains unclear. Therefore, the present dissertation will focus on three important questions considering the relation between frontal-subcortical loops and GDB. The first questions deals with the neural reward processing of incentives and its relation to the personality trait “reward sensitivity”. The second focuses on neural reward processing in schizophrenia. The third question regards the correlation between neural activation during motor inhibition and the personality trait of impulsivity.

The studies presented here aim at further exploring the influence of prefrontal-subcortical networks on interindividual differences in GDB. As a number of neuropsychiatric diseases originate from dysfunctional activity in the aforementioned circuits, this research provides further input for psychopathological and etiological models of these disorders.

The following section will provide a brief overview of theoretical considerations regarding GDB and its relation to schizophrenia. The neural correlates of these concepts will be outlined in the context of frontal-subcortical networks. After a description of the methodological approach used in the three studies, an overview of the research questions and the obtained results of these studies will be given. The obtained findings will then be summarised and some future directions will be outlined. Each study is presented in detail as original article.

2. Theoretical and empirical background

2.1 The neural substrates of goal-directed behaviour

The ability to successfully adapt behaviour, to make decisions and to direct a specific behaviour towards a goal is mediated via a certain number of parallel but separated neural circuits. Several different circuits have been proposed, each linking distinct areas of the frontal cortex with the striatum, substantia nigra, thalamus and globus pallidus (Bechara et al., 2000; Mega & Cummings, 1994; Ragozzino, 2007; Tekin & Cummings, 2002). Two circuits involving the supplementary motor area as well as the frontal eye fields are thought to mediate motor functions. The dorsolateral prefrontal cortex (DLPFC), the orbitofrontal cortex (OFC) and cingulate cortex regulate executive functions, integration of emotional information into behavioural responses and motivated behaviour, respectively (Alexander et al., 1986).

Out of the many aspects of GDB, we will here focus on three major domains and their associated circuits; processing of rewards, inhibition of unwanted responses and the influence of a psychiatric disorder. Schizophrenia and its common observed symptoms of apathy, anhedonia and depression are depicted in the scope of their influence on GDB. In addition to a general definition of these components, a short overview of their neural correlates is given.

2.2 Neural correlates of reward processing

A reward is a desirable outcome which induces subjective feelings of pleasure, behaviour of approach and increases the frequency as well as the intensity of behaviour that leads to reward (Schultz, 2000). The mesolimbic and mesocortical networks are dopaminergic pathways which are crucial for the processing of reward-related information. They consist of numerous regions which interact in a specific temporal manner in order to modulate behavioural responses to incentive stimuli. Striatal dopamine projections (DA) have been identified as being necessary to direct motor behaviour towards appropriate goals (Cannon & Bseikri, 2004). The monitoring of reward values is thought to be mainly mediated by the medial orbitofrontal cortex (mOFC) (Elliott et al., 2000). Accordingly, the differentiation between “wanting” and “liking” is a useful model to describe the distinct components of the neural reward system (Berridge, 1996). “Wanting” refers to appetitive and motivational components, which mediate motivational approach to specific objects, whereas “liking”

corresponds to the hedonic impact of a reward. They both have separable neural substrates which can be manipulated and measured in an independent fashion (Berridge, 2007). The ventral striatum (VS), a region which is thought to be involved in affective and motivational processing (Delgado, 2007; Robbins & Everitt, 1992), has been identified as an important region for the coding of anticipatory elements of reward processing (i.e., "wanting", Knutson et al., 2001b) Activity in prefrontal regions, more specifically the mOFC, has been linked to the “liking” of a reward (Kringelbach, 2005) (Figure 1).

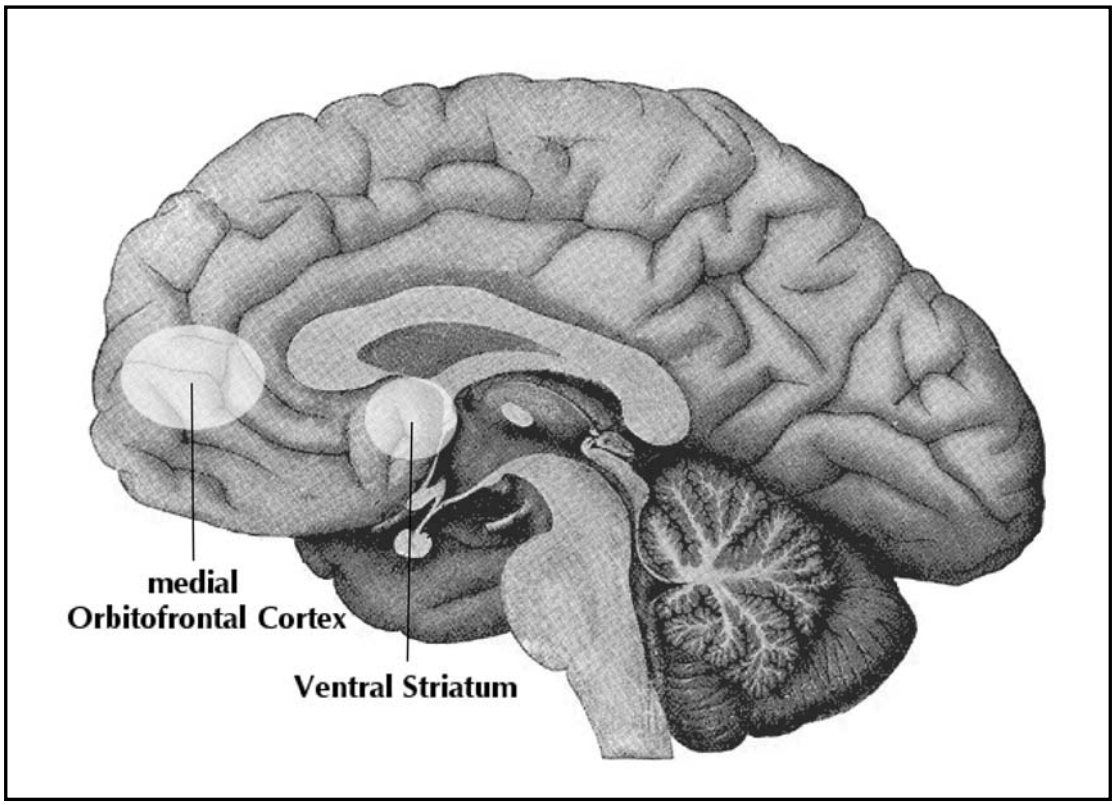

Figure 1: Approximate visualisation of the Ventral Striatum and medial Orbitofrontal Cortex. Brain sectioned in the median sagittal plane, taken and modified from the 20th edition of “Gray´s anatomy of the human body”, 1918.

One model to account for interindividual differences in the response to incentive stimuli is the Reinforcement Sensitivity Theory (RST) proposed by Gray (1970). Two behavioural systems are proposed; the behavioural activation system (BAS), which is conceptualised as a motivational system responding to rewarding and non-punishing outcomes, as well as the behavioural inhibition system (BIS), an attentional system reacting primarily to signs of punishment and non-reward. Whereas the first one activates reward-seeking behaviour promoting approach towards potential rewarding outcomes despite any risk involved, the second one leads to inhibition of appetitive responses and an increase in arousal (Corr, 2004; Gray & McNaughton, 2000). The

BAS system is thought to be mainly modulated by mesolimbic and mesocortical DA projections, whereas the BIS is related to the septo-hippocampal system and amygdala. It has been shown that trait reward sensitivity as measured by the BAS is related to activation in a frontal-striatal network during processing of food relevant images (Beaver et al., 2006), but it is still unclear how the BAS, and especially the BIS, relate to the different phases of reward processing.

2.3 Neural correlates of impulsivity

Impulsivity has been defined as a multidimensional concept incorporating failure of response inhibition, rapid processing of information, novelty seeking and the inability to delay gratification (Barratt, 1985). It is conceptualised as a personality trait which is related to drug abuse (Allen et al., 1998; Kreek et al., 2005) as well as psychiatric disorders, for example attention-deficit/hyperactivity disorder (ADHD) and obsessive-compulsive behaviour (OCD) (Chamberlain & Sahakian, 2007). Recent studies investigating the neural correlates of inhibition have used paradigms targeting response inhibition, which represents the ability to suppress a prepotent inappropriate response. The findings indicate an involvement of prefrontal areas, mainly the ventrolateral prefrontal cortex (VLPFC) and dorsolateral prefrontal cortex (DLPFC) (Aron et al., 2004; Asahi et al., 2004; Liddle et al., 2001), as well as medial frontal regions such as the pre-supplementary motor area (pre-SMA; Simmonds et al., 2008) and subcortical areas such as the subthalamic nucleus (STN; Aron & Poldrack, 2006). These results provide converging evidence for a frontal–subcortical network for response control (Aron et al., 2007).

2.4 Schizophrenia and goal-directed behaviour

A reduction of goal directed behaviour (Brown & Pluck, 2000) as well as impairments in decision making (Heerey et al., 2008) is a common observation in patients with schizophrenia. It has been shown that schizophrenic patients prefer non-goal-directed behaviours (e.g., eating, smoking) over goal-directed behaviours (e.g., making dinner, working). This finding has been explained by a deficit in anticipatory but not consummatory pleasure (Gard et al., 2007). Subsequently, it has been found that unmedicated patients and those treated with typical neuroleptics showed reduced activation of the VS during the expectation of a reward (Juckel et al., 2006a; Kirsch et al., 2007; Schlagenhauf et al., 2008), whilst processing of rewarding outcomes appears to be unaffected (Kirsch et al., 2007). The impaired functioning of

the mesolimbic dopamine system in patients with schizophrenia has been shown to be related to overall negative symptoms. More specifically, a negative correlation between VS activation during the expectation of a reward and negative symptoms has been found (Juckel et al., 2006b). Negative symptoms are a commonly occurring group of symptoms reflecting the loss of normal traits or abilities in patients with schizophrenia. The exact relation between activation during expectation/receipt of a reward and the specific subcategories of negative symptoms in schizophrenia still remains unclear. In the following section, a simple framework is proposed which aims at relating specific aspects of negative symptoms with the different stages of reward processing. Dysfunctional activations in frontal-striatal functional loops represent a vulnerability marker for schizophrenia (Morey et al., 2005), have been related to emotional disturbances observed in patients (Crespo-Facorro et al., 2001), and may account for the heterogeneity of symptoms in this disease (Robbins, 1990).

2.4.1 Apathy

Apathy has been defined as a loss of motivation leading to a lack of responsiveness to stimuli and a reduction in goal directed behaviour (Marin, 1991; Stuss et al., 2000). As the anticipation of a reward displays a strong relation to motivational processes (Schultz, 2002), apathy observed in schizophrenia could be caused by a diminished activation of the VS during the expectation of a reward. Apathy in general (i.e., occurring as a symptom in diseases such as Alzheimer, Parkinson, etc.) has been related to a frontal-subcortical circuit involving amongst others the anterior cingulate cortex and nucleus accumbens (Marshall et al., 2007). It is a frequent behavioural consequence of lesions or dysfunctions occurring in either prefrontal or basal ganglia regions (Levy & Dubois, 2006).

2.4.2 Anhedonia and depression

Anhedonia and depression are common but distinct symptoms of schizophrenia and are negatively related to experiences of positive emotions during daily life (Horan et al., 2006; Pizzagalli et al., 2005; Siris, 2000). Anhedonia, or the decreased capacity to experience pleasure, has been conceptualised as a core feature of schizophrenia (Meehl, 1962). A blunted hedonic impact of a reward, observed to occur independently from motivational components (Gard et al., 2007), may be specifically related to these symptoms, given that both are characterised by an altered reward circuitry (Holcomb & Rowland, 2007; Martin-Soelch, 2009). Frontal-striatal

abnormalities have indeed been observed in individuals with depression and anhedonia, suggesting a potential neural basis for both symptoms (Crespo-Facorro et al., 2001; Drevets et al., 2008).

2.5 Research questions

After providing a basic understanding of goal GDB and its general components, a subgroup of elements has been specified and will be investigated in the following studies. Based on the existing literature, it is assumed that (1) the sensitivity to rewards of an individual is mediated by the processing of incentives in a medial orbitofrontal – ventral striatal network, (2) the ability to inhibit unwanted motor responses relates to impulsive traits of a person, which draw upon a functional network between ventro-dorsolateral prefrontal and subcortical regions, and finally, (3) the frontal-striatal reward network is disturbed in patients with schizophrenia. These assumptions need further investigation in order to provide a clearer understanding of the functioning of the frontal-subcortical networks in question. In the following studies, functional imaging has been used in order to depict the specific neural correlates relevant in the processing of rewarding incentives and inhibition of unwanted responses. In the next section, after providing an overview of the method of functional imaging and the paradigms used in the studies, the specific research questions and results of the three studies will be summarised.

3. General methods:

3.1 Functional magnetic resonance imaging

Functional magnetic resonance imaging (fMRI) allows the non-invasive measurement of increase in oxygenated blood flow to the local vasculature that accompanies neural activity in different brain areas. Task-related cognitive functions can therefore be related to activity in specific brain regions. In the following section, the method of fMRI and the related statistical procedures used in the enclosed studies will be shortly summarised.

3.1.1 The “Blood Oxygenation Level Dependent” (BOLD) effect

fMRI allows the measurement of a direct correlate of regional cerebral blood flow, the “Blood Oxygenation Level Dependent” (BOLD) effect. It describes the change in magnetic resonance signal that occurs when levels of oxygenated (i.e., diamagnetic) as opposed to deoxygenated (i.e., paramagnetic) haemoglobin increase in areas with recent neural activity. MRI sequence parameters sensitive to changes in magnetic susceptibility allow the collection of images reflecting variations of the BOLD signal. By using statistical procedures, activation in single volume elements of these images can subsequently be related to specific aspects of cognitive tasks performed whilst collecting the data.

3.1.2 fMRI data processing

The acquired functional T2* images were processed in three steps in order to be able to make inferences about the cognitive processes underlying the aforementioned tasks. All images were collected using a 3-T Siemens Trio MRI scanner (Siemens Medical Solutions, Erlangen, Germany) equipped with a standard single channel head coil, and analysed using SPM5 (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, London, UK).

In a first step, images were “pre-processed” in order to prepare them for further statistical analyses. More precisely, the acquired images were slice-time corrected to account for differences in acquisition time between slices, and motion corrected and unwarped to account for movement of the participants during the acquisition. We then coregistered the structural T1 image of the subject’s brain to the space of the mean T2* image. Subsequently, both T1 and T2* images were spatially normalised to a standard brain template (Montreal Neurological Institute, MNI). Finally, functional

images were smoothed using an 8 mm Gaussian Kernel (10 mm in study III), which allows increasing sensitivity by averaging out uncorrelated noise across volume elements (voxels).

In a second step, images of single subjects were analysed in the context of the general linear model (GLM) approach (Friston et al., 1995). The general linear model expresses the observed response using a linear combination of explanatory variables and an error term. Intrinsic serial correlations were accounted for by 1st order auto-regression (AR(1)) and low frequency drifts were removed using a high-pass filter of 128 Hz (256 Hz in study III). A statistical model was then constructed which included regressors modelling the events of interest occurring during the respective tasks. The separate regressors were then convolved with the canonical hemodynamic response function described by Cohen (1997). Error trials as well as targets (only in study 1&2) were included as regressors of no interest. The resulting estimations of GLM parameters can then be combined in a linear fashion, allowing the assessment of changes in the BOLD signal dependent on the experimental condition. Accordingly, individual contrast images corresponding to the effects of interest were subsequently constructed.

The third step involved a random effects analysis including the contrast images of all subjects, allowing population inference (Holmes & Friston, 1998). A whole brain analysis was carried out in order to identify brain areas which activation was specifically related to the experimental conditions. One-sample t-tests were used for within-group comparisons, two-sample t-tests for comparison between groups.

3.1.3 Signal change and correlational analysis

To relate task-related brain activation with personality differences (or symptoms in patients with schizophrenia), we correlated region-specific percental signal change with individual scores in the different psychometric scales. To account for activation occurring in the VS (study 1&2) and amygdala (study 1), we used an anatomical mask retrieved from a publication based probabilistic MNI-atlas (Nielsen & Hansen, 2002, please refer to http://hendrix.imm.dtu.dk/services/jerne/ninf/voi/index-alphabetic.html, access date June 2008), allowing a more effective comparison of results between studies using the same mask (Juckel et al., 2006b; Schlagenhauf et al., 2008). As structural masks of the prefrontal cortex often tend to contain large areas subserving partially different functions, we used functional masks based on a whole brain analysis during the main contrast of interest. Accordingly, masks of the

mOFC (originating from study 1, and used in study 1 & 2) and of the VLPFC (used in study III) were constructed from a group-level contrast. Mean percent signal change from the mean of overall intensity was extracted using MarsBaR (Brett et al., 2002). Correlational analyses between signal change and scales were then performed using SPSS version 13.0.

3.2 Experimental tasks

3.2.1 Monetary incentive delay task (MID)

The MID task is used to elicit neural and affective responses to quantifiable incentives. It allows examining brain activation during the anticipation of potential monetary gain, loss or no consequences. The original task was proposed by Knutson and others (2001a), and consists out of a simple reaction time task where subjects can win money depending on their performance. A geometric shape is presented (cue), indicating the amount of money that can be won if subjects react quickly enough to a subsequently following target (e.g. white square). Between cue and target, a variable interval is included during which subjects have to wait for the target to appear (anticipation phase). Feedback about the amount of money won in the respective trial is given immediately after target presentation (receipt of reward). Thus, the task allows constructing an event related fMRI design where both anticipation and receipt of a reward can be measured independently. It is a well established paradigm and has been used in numerous studies investigating neural responses to incentives in healthy populations (e.g., Bjork & Hommer, 2007; Dillon et al., 2008; Knutson et al., 2003) and subjects with psychiatric disorders (e.g., Juckel et al., 2006b; Ströhle et al., 2008; Wrase et al., 2007).

Here we used a modified version of the MID task (Abler et al., 2005), where task difficulty is reduced to allow the use of this task in both healthy and psychiatric populations. Each subject performed 140 trials of the task, divided in two 11-minutes scan sessions. Each trial started with the presentation of a cue, indicating the amount of money subjects could win (i.e., 1 Euro, 20 Cent, 0 Euro) by responding correctly. There was a total of 36 Euro that could be won; the money was shown to the subjects before entering the scanner. After the anticipation period which lasted 3 seconds, subjects were required to correctly react to one of two symbols (i.e., triangle inclined to the left or right) with a left or right button press according to the direction of the triangle within a fixed interval of 1 second. Since the use of a fixed response-

time-frame results in a low task difficulty, we implemented a probabilistic reward pattern which entailed no reward being paid out in 40 predefined trials. Feedback was presented immediately follow target presentation. Incorrect button presses resulted in an outcome of 0 Euro, whereas a penalty of -1 Euro was applied whenever no button press occurred in a trial.

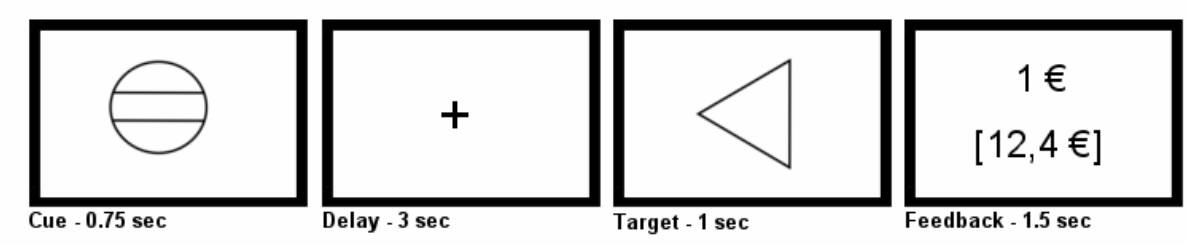

Figure 1: The MID task (Abler et al., 2005; Knutson et al., 2001a). Cues representing possible reward outcomes (1 Euro, 20 Cent, 0 Euro) and task structure of the monetary incentive delay task. Participants were first presented with a cue stipulating the amount of money they could win if they reacted correctly during the ensuing discrimination task. Immediately after target presentation, participants were informed about the money they had won during the trial and were presented with their cumulative total win so far.

3.2.2 GO/NO-GO task

The Go/No-go task is a common paradigm used to investigate response inhibition via functional imaging (Simmonds et al., 2008). It requires the subject to respond as quickly and accurately as possible to one type of stimulus (target; Go-event), while withholding the response to another type of stimulus (distractor; No-go-event). A prepotent tendency to respond is created by using a relative high number of targets (80 %) requiring inhibition in only 20% of the trials (Durston et al., 2002). In previous event-related fMRI studies, statistical analyses have been performed using contrasts between rare inhibition and frequent response trials, identifying relevant regions for inhibition in a right-sided frontal-parietal network with a key focus in right ventrolateral prefrontal cortex (e.g., Garavan et al., 1999; Wager et al., 2005). One major flaw considering the methodology of these studies is the use a design which compares two events occurring with discrepant frequencies. The appearance of a No-go event could therefore be associated with an oddball effect, which has also been associated with activation in the inferior frontal cortex (Braver et al., 2001). A further issue considers task difficulty; rare No-go trials entail a high number of commission errors whereas frequent Go trials usually lead to few omission errors (Simmonds et al., 2008). To address this issue, a modification of the original Go/No-go task has been proposed; the comparison of rare inhibition trials with rare responses (Kaiser et al., 2003; Kiefer et al., 1998). More specifically, rare no-go trials embedded in frequent Go trials (rare No-go-condition) are compared with rare Go-trials embedded in

frequent No-go trials (rare Go-condition)(see figure 2). As the previous studies have employed this paradigm using EEG measurements, we will here provide an initial adaptation of this task for fMRI.

During the functional acquisition of images, subjects were required to react as fast and accurate as possible by pressing a button when a target stimulus appeared, and to inhibit the response when a distractor stimulus was presented. Each subject was instructed to respond to one target, either square or circle, during the entire procedure. In the rare Go-condition, target stimuli appeared in 20% of the trials, whereas in the frequent Go-condition, target stimuli appeared in 80% of the trials, thus building up a prepotent response tendency. Subjects were informed before each block if frequent or rare responses would be required, in order to avoid a change of task set during the block.

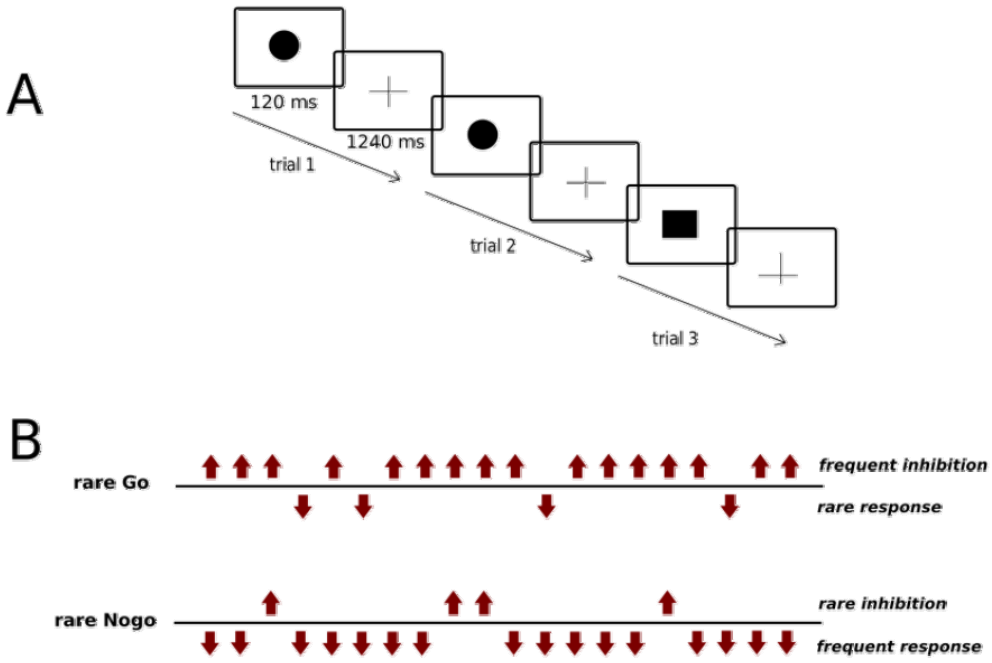

Figure 2: The Go/No-go task. A) Example sequence of stimulus presentation. B) Frequency of trials in the rare Go-condition (20% rare responses, 80% frequent inhibitions) and the frequent Go condition (80% frequent responses, 20% rare inhibitions).

4. Summary of studies I,II,III

In order to further explore the role of prefrontal-subcortical networks in GDB, the following three topics will be explored in the enclosed studies using fMRI. The following subjects are concerned:

I. the relation between the personality trait “reward sensitivity” and the neural reward network, i.e., a functional brain network encompassing medial-orbitofrontal PFC regions as well as subcortical striatal regions.
II. the influence of negative symptoms, i.e. apathy, depression and anhedonia, on neural reward processing in patients with schizophrenia.
III. the correlation between activity of the dorso-ventrolateral prefrontal cortex and impulsivity during the inhibition of prepotent motor responses.

These are the main issues of the three fMRI studies presented in detail as original articles. In the following section, a brief overview will be given on the specific research questions of each of the studies and the obtained results will be shortly summarised.

4.1 Study I: “Neural reward processing is modulated by approach- and avoidance-related personality traits (Simon et al., 2010)”

Research Question:

The aim of Study I was to investigate the relationship between personality traits and neural reward processing in healthy subjects. Prior research has demonstrated the importance of abnormal reward processing in psychiatric disorders (e.g., Bjork et al., 2008; Juckel et al., 2006b). But in order to draw conclusions about reward related processing in general, less extreme interindividual variations occurring in a normal, non-pathological range need to be taken into account. Only a limited number of studies have focussed on the relation between personality aspects and neural reward processing, demonstrating that elements such as impulsivity or extraversion, risk aversion or academic motivation can exert modulatory influences on reward processing (Cohen et al., 2005; Martin & Potts, 2004; Mizuno et al., 2008; Tobler et al., 2007). The Reinforcement Sensitivity Theory (RST, Gray, 1970) is a biologically based personality model postulating two behavioural systems mediating individual differences in appetitive functioning, namely the behavioural activation system (BAS) and the behavioural inhibition system (BIS). The BAS represents a motivational system which responds to rewarding and non-punishing stimuli (Corr, 2004), and the

BIS is considered an attentional system sensitive to signal of punishment and promoting inhibition of appetitive responses (Gray & McNaughton, 2000). Mesolimbic and mesocortical dopamine projections (DA) have been postulated as the neural basis of the BAS, whereas the BIS is thought to mainly modulated via the septo-hippocampal system (Smillie, 2008). It is still not clear how both systems are specifically related to the mesocortical and mesolimbic reward circuitry.

To this end, we employed fMRI to directly explore the relationship between the different stages of reward processing (assessed via the MID task) and reward sensitivity (i.e., BAS and BIS). High BAS scores have been associated with impulsivity (Gray, 1987) and subjects with ADHD have shown less striatal activation during the expectation of a reward, but more activation in the mOFC during the receipt of a reward (Ströhle et al., 2008). Low BAS scores have been linked to depression, which was found to induce less striatal activation during the receipt of a reward (Steele et al., 2007). We therefore expected that individuals with high BAS show less VS activation during the expectation of a reward, but more VS and mOFC activity during the receipt of a reward than those with low BAS scores. High BIS scores have been related to a higher level of anhedonic symptoms (Hundt et al., 2007), we therefore expected the neural processing of rewarding outcomes to be reduced in subjects with high BIS scores.

Results and discussion:

Subjects reacted faster when a 1 Euro reward was promised than during the 0 Euro or 20 Cent conditions. The contrast “Anticipation of reward versus anticipation of no reward” revealed increased activation in the right VS including the nucleus accumbens. The analysis of the contrast “Receipt of a reward versus receipt of no reward” revealed increased activation in the mOFC and right VS. The observed neural activations are in line with other findings from prior studies investigating the neural correlates of reward processing (e.g., Abler et al., 2005; Knutson et al., 2003). Additionally, we found a significant positive correlation between BAS scores and VS activation during the receipt of 1 Euro, as well as a positive correlation between BAS scores and mOFC activation during the receipt of and omission of 1 Euro. The BIS scale was negatively correlated with VS activation during the receipt of 1 Euro. Our findings indicate that a high BAS leads to a higher responsiveness to the receipt of rewards whilst reducing the reactivity to negative outcomes. This extends findings

from ADHD to individual differences in a normal, non-pathological range. A low BAS, on the other hand, leads to a lower hedonic reactivity to rewards. This further supports the often made association with depression, as our results are similar to observations made in patients with this disorder (Steele et al., 2007). We did not observe correlations between BIS scores and activity in the amygdala, a structure which has been proposed as a key component of the BIS (Smillie, 2008). This could in part be due to the non-aversive properties of our task, leading to low levels of anxiety. Nonetheless, the observed correlation between BIS and VS activity indicates an attenuating influence on the mesolimbic reward circuitry. Taken together, the results of this study indicate that individual differences in approach and avoidance tendencies can indeed be measured on a neural level of appetitive functioning.

4.2 Study II: "Neural correlates of reward processing in schizophrenia – Relationship to apathy and depression (Simon et al., 2010)"

Research Question:

In schizophrenia, dysfunctional activation of the mesolimbic dopamine system has been observed in previous research and is considered an important element in its pathophysiology (Abi-Dargham et al., 2000; Juckel et al., 2006b; Waltz et al., 2008). Studies employing the MID task have found that in both unmedicated patients and those treated with atypical neuroleptics, activation of the VS during the anticipation of a reward is impaired (Juckel et al., 2006a; Kirsch et al., 2007; Schlagenhauf et al., 2008). Furthermore, a negative correlation between VS activation and negative symptoms has been observed in unmedicated patients with schizophrenia (Juckel et al., 2006b). In contrast, neural activation during the receipt of a reward has received less attention, leaving the nature of impairment in the different stages of neural processing as a matter of debate. The objective of study II was twofold: one aim was to investigate the differences in neural activation between healthy subjects and patients with schizophrenia during both anticipation and receipt of a reward, and the second aim was to related neural activations in schizophrenic patients to specific aspects of negative symptoms. As figure 2 illustrates, we postulated that deficits in VS-activation during the anticipation of a reward could be specifically related to apathy, a symptom which has been described as a loss of motivation leading to a reduction of goal-directed behaviour (Marin, 1991). Furthermore, both depression and anhedonia, frequent symptoms of schizophrenia (Horan et al., 2006; Siris, 2000), have been related to an altered reward circuitry (Holcomb & Rowland, 2007; Martin-

Soelch, 2009). Blunted neural responses to rewarding outcomes could be therefore be related to these symptoms.

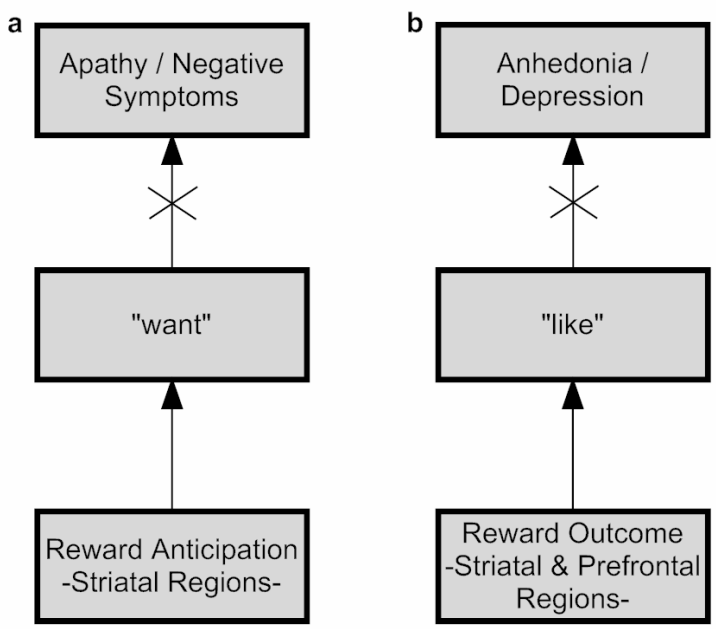

Figure 3: Theoretical assumptions of study II. (a) Dysfunctional activation of the VS during the expectation of a reward is related to apathy in schizophrenia. (b) Dysfunctional activation of the mOFC during the receipt of a reward is coupled to symptoms of anhedonia and/or depression.

Results and discussion:

There were no significant differences between healthy subjects and patients with schizophrenia concerning reaction times or amount of money earned. Additionally, there was no significant difference in neural activation between groups. Both showed comparable neural activation during the expectation and receipt of a reward than those observed in study I. Nevertheless, we observed a negative correlation between apathy and activation of the VS during reward anticipation as well as a negative correlation between depression and activation of the VS during receipt of a reward. Apathy might therefore be a key manifestation of dysfunctional VS activity during expectation of a reward, as overall negative symptoms did not show such a relationship. Furthermore, the neural coding of pleasurable outcomes in the VS may contribute to the neurobiological origin of depression in the context of schizophrenia. Since we did not find any correlation between anhedonia and neural activity, our study further corroborates the recently established idea that anhedonic symptoms in schizophrenia are not directly related to hedonic processing, but may rather be secondary to motivational deficits (Wolf, 2006). In summary, whilst there were no significant differences between healthy subjects and patients with schizophrenia, we

did observe distinct relations between specific symptoms and neural activation. This indicates that a differentiation of common negative and depressive symptoms in schizophrenia might be important for understanding their relationship with dysfunctional reward processing.

4.3 Study III: "Motor impulsivity and the ventrolateral prefrontal cortex (Goya-Maldonado et al., in revision)"

Research Question:

Response inhibition is a construct of clinical importance (Weisbrod et al., 2000) which has been related to an inferior/medial frontal-subcortical network. Unfortunately, methodological problems still prevent a consensus about the exact functions of the different regions relevant for response inhibition. In order to prevent the recruitment of confounding cognitive processes such as oddball effects or task difficulty, a variant of the Go/No-Go task was used to compare inhibitions with responses occurring in an equiprobable manner and during the same scanning run, while still allowing the "classical" contrast of rare inhibitions versus frequent responses. Based on previous research, it was expected that the comparison of rare inhibition versus frequent response (i.e., the "classical" comparison) would lead to activation of the right VLPFC, whereas the comparison of rare inhibition versus rare response was expected to lead to bilateral VLPFC activations (Kiefer et al., 1998). Furthermore, the relation between impulsivity (assessed via the Baratt Impulsiveness Scale 11 (BIS, Patton et al., 1995)) and brain activation during motor inhibition was expected to be located in the right VLPFC and DLPFC (Asahi et al., 2004; Horn et al., 2003; Passamonti et al., 2006). Conclusively, study III aimed at investigating the relationship between motor impulsivity and brain activation during response inhibition (i.e., performance during a Go/No-go task) employing event-related fMRI.

Results and discussion:

Subjects performed better in the rare-Go condition than in the rare Nogo condition, a finding which was not related to the BIS-scores. Analysis of fMRI data revealed clusters of activation in the bilateral VLPFC and the nucleus subthalamicus for the comparison between rare inhibitions versus rare responses. Additionally, the BIS motor impulsivity subscale showed a significant correlation with left and right VLPFC signal change assessed during the rare No-go condition.

The main finding of this study is that motor impulsivity is positively related to bilateral VLPFC activation during inhibition trials. The missing positive correlation between the behavioural results and impulsivity indicates that subjects with higher impulsivity were not impaired in the task. Higher recruitment of the VLPFC could therefore reflect a compensatory mechanism in subjects with high motor impulsivity in order to be able to maintain task performance. As prior research found a negative correlation between the DLPFC and motor impulsivity (Asahi et al., 2004), we suggest that the VLPFC and DLPFC have different functional roles in response inhibition tasks.

5. General Discussion

The three studies presented in this dissertation each use the method of fMRI to explore the relationship between frontal-subcortical networks and interindividual differences in GDB.

Study I found specific relations between the behavioural approach and avoidance system and both the VS and mOFC during the receipt and omission of a reward. Stronger neural activation during the receipt of a reward could indicate that a high behavioural approach tendency leads to a higher saliency for positive outcomes. Although deactivations are more difficult to interpret, a lower reactivity to negative outcomes (i.e., omission of an expected reward) could indicate a reduced amount of negative emotions. The results are similar to those observed in patients with ADHD, where an increased effect of rewarding outcomes has been observed (Ströhle et al., 2008). The observation that a low behavioural activation tendency leads to a lower reactivity to rewards as well as a stronger deactivation during the omission of a reward, is similar to results observed in patients with depression (Steele et al., 2007), thus further corroborating the association between a low approach motivation and depression. A high behavioural inhibition tendency led to a lower reactivity to rewarding outcomes, indicating the attenuating influence of this system on the mesolimbic reward circuitry. Study I provides a first account on the relation between the neural reward circuitry and the behavioural approach/inhibition systems.

The main objective of study II was to relate symptoms of schizophrenia to the neural processing of rewards. It has been shown that schizophrenic patients exhibit impairments in different aspects of the reward system (Gold et al., 2008). In contrast to overall negative symptoms, we found that the specific symptom apathy is negatively related to activation of the VS during the expectation of a reward. Apathy might thus be more closely related to the neural network processing rewards than other negative symptoms. During the receipt of a reward, depressive symptoms were negatively related to VS activation, thus indicating that the neural coding of pleasurable outcomes might contribute to the origin of depression in the context of schizophrenia. The missing observation of a modulatory influence of neural reward processing on the assessed symptom of anhedonia might be explained by methodological constraints. On the one hand, the scales used in this study and activity in the specific brain regions may be related to different concepts, on the other hand, it could be due to the fact that the scale used to assess anhedonia did not

differ between anticipatory and consummatory pleasure. This allows the assumption that psychometrically assessed anhedonia in schizophrenia is not directly linked to hedonic processing, but may rather be secondary to motivational deficits (Wolf, 2006). Finally, study II indicates that in order to further specify the role of a dysfunctional reward network in the pathogenesis of schizophrenia, a differentiation of common negative and depressive symptoms is needed.

In study III, the behavioural performance in the experimental task was not related to interindividual differences in impulsivity. Thus, the positive correlation between motor impulsivity and activations in the VLPFC indicates a stronger recruitment of this region in order to allow an appropriate inhibition of inappropriate responses in impulsive subjects. Prior research has found a negative correlation between motor impulsivity and activation in the DLPFC (Asahi et al., 2004). Furthermore, previous studies found no correlation between neural activation and the global score of the scale assessing inhibition, which includes aspects of attentional and non-planning impulsiveness (Horn et al., 2003; Passamonti et al., 2006). In addition to our own results, this indicates that different components of impulsivity have different neural correlates. Overall, study III provides a further specification of the relation between impulsivity and the related neural networks, allowing a more precise assessment of this construct in consequent studies investigating patients with psychiatric disorders.

Taken together, the three studies emphasize the importance of frontal-subcortical circuits in GDB, both in clinical and non-clinical populations. We showed that the exact role of the functional networks of the human brain can only be specified by taking into account interindividual differences. Accordingly, study I found that a medial orbitofrontal/ventral striatal network is specifically related to behavioural approach and inhibition tendencies, with different, quantifiable contributions of the two regions. Study II showed that impairments in the VS, part of the mesolimbic reward network, can lead to symptoms of apathy and depression in patients with schizophrenia. Additionally, study III identified a correlation between activity in ventrolateral regions of the prefrontal cortex and motor inhibition during successful inhibition of unwanted responses.

Prior research has begun to highlight the involvement of frontal-subcortical circuits in a variety of neuropsychiatric diseases, including schizophrenia (Carlsson, 2006), suggesting that its psychopathology is associated with aberrant intrinsic organization of functional brain networks (Winterer, 2004). By conceptualising neuropsychiatric

disorders as circuit dysfunctions, one can assume that the same syndrome can be observed with involvement of several structures of the circuit (Tekin & Cummings, 2002). Accordingly, we observed connections between personality aspects and activation in both the basal ganglia and prefrontal cortex in study I and study III, whereas we did only observe this relation with subcortical regions in study II. These results illustrate the differential involvement of brain regions in specific behavioural aspects, observations which need to be taken into account when constructing an integral theory of functional brain networks.

As we did not observe any relation between reward related neural activity and anhedonia in schizophrenia patients, we conclude that approach motivation might be a better index for hedonic response on a neural level than anhedonia scales (Germans & Kring, 2000). Although the self-rating scale used in study II for the assessment of anhedonia in patients with schizophrenia is limited due to its failure to differentiate between anticipatory and consummatory hedonic reactivity as well as its possible confusion with the ability to recall and relate to previous experiences (Horan et al., 2006), we agree with previous authors arguing that anhedonia might be a result of abated motivational reactivity rather than a decrease in hedonic feelings per se (Wolf, 2006).

Methodological issues could possibly limit the interpretation of the results of the three studies. Besides the above mentioned use of an anhedonia self-rating scale with limited validity in study II (Physical and Social Anhedonia scale, Burgdörfer & Hautzinger, 1987; Chapman et al., 1976), the heterogeneous medication of patients in this study constitutes another limitation. A more general constraint, considering all three studies is the use of correlational analyses in order to relate the assessed personality traits or symptoms with neural activity. Although we took great care to avoid non-independence errors (Vul et al., 2009), correlations do not allow detecting a direct causal relation and, therefore, have to be interpreted with caution.

Altogether, the present dissertation shows that frontal-subcortical circuits can provide an integrative framework for understanding cognitive and emotional functions in healthy subjects as well as in psychiatric disorders. Supplying exact definitions of the specific functions and dependencies of the network’s components in healthy subjects provides a necessary basis for research dealing with personality traits and psychiatric symptoms. This framework can then help us to understand symptoms as variations of normal mental and neural processes.

6. Abstract

Goal-directed behaviour consists of instrumental actions, which are performed in order to achieve a desired outcome. It has been shown that these actions do not solely depend on action-outcome contingencies, but are also strongly influenced by personality traits or psychiatric disorders such as schizophrenia. Sensitivity to rewards and impulsivity have been identified as prominent factors, though the exact relation still remains unclear. Therefore, the goal of this dissertation is to provide an additional specification of interindividual differences in goal-directed behaviour on a neural level.

Using functional imaging, we employed two different paradigms to probe reward-related as well as inhibition-related neural activation in healthy subjects and patients with schizophrenia. Study I investigated the neural response during a monetary incentive delay task in 23 healthy subjects, relating the observed brain activation to psychometrically assessed traits of behavioural approach/inhibition. We found that the tendency to approach reward-related situations leads to an elevated neural response to positive outcomes and an attenuated response to omissions of reward. Additionally, a high behavioural inhibition tendency led to an attenuated response to rewards. Study II applied the monetary incentive delay task in a group of 15 patients with schizophrenia. The results demonstrate a negative relation between striatal activation during the expectation of reward and the symptom of apathy. In addition, a negative relation was found between striatal activation during the receipt of a reward and the symptom of depression. Study III investigated the relation between the personality trait of impulsivity and brain activation during the inhibition of inappropriate responses. Results showed that impulsivity is positively related to activations of bilateral ventrolateral prefrontal regions.

The results illustrate the importance of frontal-subcortical networks in goal-directed behaviour in clinical and non-clinical populations. An orbitofrontal/striatal network is specifically related to behavioural approach and inhibition tendencies, whereas impairments in the ventral striatum can lead to symptoms of apathy and depression in patients with schizophrenia. Additionally, activation in ventrolateral prefrontal regions is related to motor inhibition during successful inhibition of unwanted responses. Providing exact definitions of the specific functions and dependencies of frontal-subcortical circuits can inform our understanding of personality traits and symptoms as variations of normal mental and neural processes.

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Appendix A: Curriculum Vitae

Personal Data:

Name: Joe Jacques Simon

Date of birth: 22.06.1981

Place of birth: Luxembourg

Family Status: single

School Career:

1987 – 1993	Primary school, Cents, Luxembourg
1993 – 2000	Secondary school, Lycée Robert Schumann, Luxembourg
2000	A-Levels

Academic Career:

2000 – 2002	Basic study period Psychology, “Centre Universitaire de Luxembourg
2002–2006	Main study period Psychology, University of Konstanz, Germany
2003–2004	Internship during six months at University Clinic of Heidelberg, department of Medical Psychology
2006	Diploma in Psychology (Dipl.-Psych.)
since 2007	PhD student, Research training program “Goals and Preferences”, University of Heidelberg, Germany
since 2007	Certified Research Assistant, University of Heidelberg, Germany

Publications:

Simon JJ., Biller A., Walther S., Roesch-Ely D., Stippich C., Weisbrod M., Kaiser S. (2010). Neural correlates of reward processing in schizophrenia - Relationship to apathy and depression. *Schizophrenia Research* (2010), doi:10.1016/j.schres.2009.11.007

Simon JJ., Walther S., Fiebach CJ., Friederich HC., Stippich C., Weisbrod M., Kaiser S. (2010). Neural reward processing is modulated by approach- and avoidance-related personality traits. *NeuroImage* 49(2), 1868-1874

Goya-Maldonado R., Walther S., Simon JJ., Stippich C., Weisbrod M., Kaiser S. (2009). Motor impulsivity and the ventrolateral prefrontal cortex. *Psychiatry Research Neuroimaging* (in revision).

Conference Presentations:

Simon JJ., Walther S., Fiebach CJ., Friederich HC., Stippich C., Weisbrod M., Kaiser S. (2009). Neural reward processing is modulated by approach- and avoidance-related personality traits. Poster: Symposium at the Institute of Immunology, Luxembourg (Luxembourg).

Simon JJ., Walther S., Fiebach CJ., Friederich HC., Stippich C., Weisbrod M., Kaiser S. (2009). Neural reward processing is modulated by approach- and avoidance-related personality traits. Poster: Tagung experimentell arbeitender Psychologen, TeaP, Jena (Germany).

Simon JJ., Biller A., Walther S., Roesch-Ely D., Stippich C., Weisbrod M., Kaiser S. (2009). Neural correlates of reward processing in schizophrenia - relationship to apathy and depression. Poster: Society for Neuroscience, 39th Annual Meeting 2009, Chicago (USA).

Simon JJ., Biller A., Walther S., Roesch-Ely D., Stippich C., Weisbrod M., Kaiser S. (2009). Neural correlates of reward processing in schizophrenia - relationship to apathy and depression. Poster: The 15th Biennal Winter Workshop in Psychoses, Barcelona (Spain)

Appendix B: Declaration

Erklärung gemäß § 8 Abs. 1 Buchst. b) der Promotionsordnung der Universität Heidelberg für die Fakultät für Verhaltens- und Empirische Kulturwissenschaften

Ich erkläre, dass ich die vorgelegte Dissertation selbstständig angefertigt, nur die angegebenen Hilfsmittel benutzt und die Zitate gekennzeichnet habe.

Erklärung gemäß § 8 Abs. 1 Buchst. c) der Promotionsordnung der Universität Heidelberg für die Fakultät für Verhaltens- und Empirische Kulturwissenschaften

Ich erkläre, dass ich die vorgelegte Dissertation in dieser oder einer anderen Form nicht anderweitig als Prüfungsarbeit verwendet oder einer anderen Fakultät als Dissertation vorgelegt habe.

Name, Vorname_____

Datum, Unterschrift_____

Appendix C: Original Articles

I. Simon, J. J., Walther, S., Fiebach, C. J., Friederich, H., Stippich, C., Weisbrod, M., Kaiser, S. (2010). Neural reward processing is modulated by approach- and avoidance-related personality traits. *NeuroImage* 49(2), 1868-1874

II. Simon, J.J., Biller, A., Walther, S., Roesch-Ely, D., Stippich, C., Weisbrod, M., Kaiser, S. (in press) Neural correlates of reward processing in schizophrenia — Relationship to apathy and depression, *Schizophrenia Research* (2010), doi:10.1016/j.schres.2009.11.007

III. Goya-Maldonado, R., Walther, S., Simon, J.J., Stippich, C., Weisbrod, M., Kaiser, S. Motor impulsivity and the ventrolateral prefrontal cortex. *In revision at Psychiatry Research Neuroimaging*

NeuroImage 49 (2010) 1868–1874

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Neural reward processing is modulated by approach- and avoidance-related personality traits

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ARTICLE INFO

Article history:
Received 25 April 2009
Revised 10 September 2009
Accepted 14 September 2009
Available online 18 September 2009

ABSTRACT

The neural processing of reward can be differentiated into two sub-components with different functions, "wanting" (i.e., the expectation of a reward which includes appetitive and motivational components) and "liking" (i.e., the hedonic impact experienced during the receipt of a reward), involving distinct neural systems. We hypothesize that variability in neural reward processing previously observed in healthy subjects could reflect inter-individual differences in personality. Therefore, the aim of this study was to investigate how the neural processing during expectation and reception of a reward depends on interpersonal differences in reward sensitivity, more specifically the tendency to approach vs. avoid reward-related situations. We employed event-related functional magnetic resonance imaging during a monetary incentive delay task. Subjects with a high approach motivation showed more activation of the Ventral Striatum (VS) during the receipt of a reward, and more medial orbitofrontal activity during both the receipt and omission of a reward. Subjects with a high behavioral inhibition showed less activation in the VS during the receipt of a reward. These findings indicate that the tendency to approach or avoid reward-related situations exhibits a distinct relation with neural reward processing. Specifically, subjects with high behavioral approach appear to be sensitive mainly to positive outcomes and to a lesser extent to the omissions of rewards, whereas subjects with low behavioral approach as well as those with a high inhibition tendency display a blunted response to rewards.

Introduction

The neural substrates mediating reward involve numerous regions of the mesolimbic and mesocortical reward circuitry which interact in a specific hierarchical and temporal manner. One model to describe the distinct components of these processes is the differentiation between wanting and liking, which has been first proposed by Berridge (1996), and has received support from both neuropsychological (Pecina, 2008) and behavioral studies (Finlayson et al., 2007). Specifically, "wanting" includes appetitive and motivational components, mediating changes in behavior from active seeking to active ignoring of an object. Liking, in contrast, corresponds to pleasure related to reward, i.e. the "hedonic impact" of a reward. Wanting and liking have separable neural substrates, which can be manipulated and measured in an independent fashion (Berridge, 2007).

A growing number of studies are dealing with the neuronal processing of incentives and provide a clearer image of the neural substrates of reward processing (e.g. Bjork et al., 2004; Knutson et al., 2001b). The medial orbitofrontal cortex (mOFC), often labeled the ventromedial prefrontal cortex (Damasio and Anderson, 1985), has been identified as a prominent region for the processing of hedonic impact (Kringelbach, 2005). On the other hand, the ventral striatum (VS) is considered a primary locus for the coding of the prediction error, which is important for learning stimulus-reward associations and action selection for the obtainment of rewards (McClure et al., 2004; Schultz et al., 1997).

Recent research has focused on the influence of inter-individual differences on the neural processing of reward, mainly investigating clinical populations and demonstrating the importance of abnormal reward processing in psychiatric disorders such as mania (Abler et al., 2008), substance dependence (Bjork et al., 2008), and schizophrenia (Juckel et al., 2006). However, in order to be able to make inferences

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doi:10.1016/j.neuroimage.2009.09.016

about reward-related processing in a general population of healthy subjects, less extreme inter-individual variations on the normal, non-pathological range should be taken into account. Personality aspects, or traits, can account for a large portion of variance in behavior. Therefore, it is not surprising that individual differences in the neural processing of emotional stimuli have been found in previous studies investigating the reaction of healthy subjects to emotional faces (e.g., Canli et al., 2002), food (e.g., Beaver et al., 2006), odors (e.g., Vaidya et al., 2007), and affective pictures (e.g., Caseras et al., 2006). However, the relationship between inter-individual differences in personality and the neural processing of reward remains unclear, since only a limited number of studies have dealt with this issue. It has been found that neural reward processing can be modulated by individual differences in both impulsivity and extraversion (Cohen et al., 2005; Martin and Potts, 2004), as well as by risk aversion and academic motivation (e.g. Mizuno et al., 2008; Tobler et al., 2007).

A prominent, biologically based personality model dealing with individual differences in appetitive functioning, i.e. with the response to incentives, is the Reinforcement Sensitivity Theory (Gray, 1970). Gray's neuropsychological theory postulates two behavioral systems which mediate individual differences in response to incentive (i.e. reinforcing) stimuli (Pickering and Gray, 2001). The behavioral activation system (BAS) is conceptualized as a motivational system which primarily responds to stimuli of reward and non-punishment (Corr, 2004). It activates reward-seeking behavior and has been associated with feelings of exaltation, resulting in an approach to reward despite risks involved. In contrast, the behavioral inhibition system (BIS) is considered an attentional system sensitive to signals of punishment and non-reward, promoting inhibition of appetitive responses and an increase in arousal and attention to relevant cues (Gray and McNaughton, 2000). Extreme reactivity of both systems has been linked to psychopathological disorders. A high level of BAS is characteristic for subjects with attention-deficit/hyperactivity disorder (ADHD) (Mitchell and Nelson-Gray, 2006), whereas a low level has been associated with depression (Meyer et al., 1999). High activation of BIS is linked to anxiety-related disorders (Muris et al., 2001) and to a lesser extent with depression (Kasch et al., 2002).

Considering the neural bases of the BIS/BAS systems, it has been suggested that the BAS is mainly mediated via mesolimbic (including the ventral striatum) and mesocortical (including the prefrontal cortex) dopamine (DA) projections and that the BIS is related to the septo-hippocampal system and the amygdala (Smillie, 2008). Although contradictory findings have been reported (Reuter et al., 2004), there is some direct evidence for the role of DA projections in the BAS (e.g. Barrós-Loscertales et al., 2006). However, it is not clear how specifically the mesocortical and mesolimbic reward circuitry relates to the BAS and BIS. Here, we use functional magnetic resonance imaging (fMRI) to directly explore the relationship between reward-related neuronal processing and motivation-related personality traits, i.e., BAS and BIS. To this end, we employed the well-established monetary incentive delay task allowing the measurement of neuronal responses occurring during both expectation and receipt of reward as well as during the omission of reward (Abler et al., 2005; Knutson et al., 2001a) (cf. Fig. 1).

Based on the postulated link between the BAS and reward-related processing structures, we expected to observe a distinct connection between behavioral approach tendencies and striatal (during expectation and receipt of a reward) as well as prefrontal (during the receipt of a reward) activations. Specifically, the BAS has been associated with impulsivity (Gray, 1987), and it has been observed that individuals suffering from ADHD show less striatal activations during the anticipation, but more orbitofrontal activation during the receipt of a reward (Ströhle et al., 2008). Oppositely, depression, which has been linked to low BAS, leads to less striatal activity during the receipt of a reward (Steele et al., 2007), and has been specifically

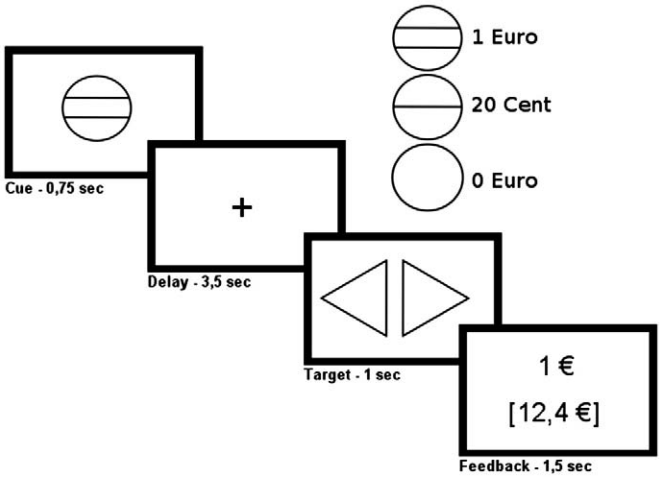

Fig. 1. Cues representing possible reward-outcomes (1 Euro, 20 cents and 0 Euro) and task structure of the delayed incentive task used during training and scanning. Subjects first saw a cue and expected to win the aforementioned amount with an unpredictable probability if they reacted correctly during the discrimination task. Immediately after target presentation, subjects were informed about the amount of money they had won during this trial and their cumulative total win was displayed in brackets (Abler et al., 2005).

associated with reduced reward responsiveness (Henriques and Davidson, 2000). We therefore expected individuals with high BAS to show less striatal activation during the anticipation of a reward, but more striatal and orbitofrontal activation during the receipt of a reward than low BAS individuals. On the other hand, as a high BIS has been found to be related to a higher level of anhedonic symptoms (Hundt et al., 2007), neural processing of rewarding outcomes was expected to be reduced in high BIS subjects. Although our task was not primarily designed to elicit amygdala activation, we conducted an exploratory analysis between BIS and activity in the amygdala, because this structure has been proposed to be key component of the BIS (Smillie, 2008).

Methods

Subjects

Twenty-four right-handed healthy university students (13 females, mean age 24.8 ± 3.2) were recruited as participants. All had normal or corrected to normal vision and were screened for neurological or psychiatric disorders using the Symptom Check List 90 Revised (Schmitz et al., 2000). All participants were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). The present study complies with the Code of Ethics of the World Medical Association (Declaration of Helsinki, version 2004) and was approved by the Ethics Committee of the Medical School of the University of Heidelberg. Written informed consent was obtained from all participants after the procedures had been fully explained.

Questionnaires

Before entering the scanner, subjects filled out a German version of the Behavioral Inhibition/Behavioral Approach Activation Scales (BIS/BAS) (Strobel et al., 2001). The four-dimensional solution of the BIS/BAS-scales as originally proposed by Carver and White (1994), which includes a BIS factor as well as three subscales which together form the BAS factor ("Drive", "Reward Responsiveness", and "Fun Seeking"), was not considered in our analysis as data from the German Version indicates that a two factor solution is to be preferred (Strobel

et al., 2001). Thus, the German version used here had two factors, a single BAS-scale including the three subscales and the BIS-scale. The mean score of the BAS was 40.2 (SD 3.9), for the BIS 20.3 (SD 3.6), which is comparable to other studies using larger samples drawn from a general population (Carver and White, 1994; Holzwarth and Meyer, 2006). Consistent with previous reports (Carver and White, 1994), we observed no significant correlation between the BIS and BAS scales ($r = .01$, $p = 0.9$).

Monetary incentive delay task (MID)

A modified version of the "monetary incentive delay task" (MID) as proposed by Abler and colleagues was used (Fig. 1) (Abler et al., 2005; Knutson et al., 2001a). This paradigm has proven to be an effective fMRI-probe to elicit both anticipation and consumption of reward. Before entering the scanner, the experimental procedure as well as the MID-task was explained to the subjects and they were shown the money they could earn by performing the task successfully in the scanner. All subjects correctly believed that they would receive the earned money (up to 36 Euro) at the end of the experiment. Once in the scanner, subjects performed a practice version of the task lasting 3 min for which they did not receive payment. Subjects engaged in two 11 min sessions of the MID task (consisting of 70 trials each) during functional scan acquisition.

Each trial started with the presentation of a symbol ("cue", 750 ms) indicating the amount of money they could win with a correct response (i.e., 1 Euro, 20 cents, or 0 Euro). After an expectation period ("delay", 3000 ms) subjects had to correctly react to one of two symbols ("targets"; i.e., triangle inclined to the right or a triangle inclined to the left) with a left or right button press corresponding to the direction of the triangle (index or middle finger of dominant hand) within a fixed interval of 1 s. This leads to a low task difficulty with a very high success rate, i.e. the rate of reward vs. non-reward depended little on the subject performance. Instead we used a probabilistic reward pattern, i.e. reward was not paid out in 40 predefined trials (out of the 100 reward trials), in order to guarantee a steady rate of reward vs. non-reward throughout all subjects. This procedure allows using reaction times as measure of motivation (Abler et al., 2007). Immediately after target presentation, feedback appeared ("feedback", 1500 ms), notifying subjects about the amount of money they had won and about their cumulative total. Incorrect button press resulted in an outcome of 0 Euro. To ensure that subjects responded in every experimental condition, a penalty of −1 Euro was applied if no button press occurred in a trial.

In order to increase statistical efficiency, trials were separated by jittered intertrial intervals (ITIs) ranging from 1 to 8 s, with a mean of 3.5 s (Dale, 1999). Once out of the scanner, subjects retrospectively rated how they felt when seeing each of the three cues and two targets on the dimensions valence and arousal, using a 9-point SAM [self-assessment manikin, Bradley & Lang (1994)].

fMRI acquisition

Images were collected using a 3-T Siemens Trio MRI scanner (Siemens Medical Solutions, Erlangen, Germany) equipped with a standard single channel head coil. The subjects performed two functional runs lasting 12 min each with 347 volumes per run. In order to minimize susceptibility artifacts in the orbitofrontal cortex 33 oblique slices with a 45° angle relative to the AC-PC-axis were acquired with the following parameters: TR = 2000 ms, TE = 30 ms, resulting in an in-plane resolution of $3 \times 3 \times 3$ mm^3, flip angle = 80°, field of view = 192×192 mm. Participants viewed visual stimuli on a projection screen via a mirror fixed to the head coil and responded with the right hand using a button box. Following the functional scans, high-resolution T1 MPRAGE anatomical images were acquired (176 slices, voxel size $1 \times 1 \times 1$ mm, TR 11 ms, TE 4.92 ms, 15° flip angle) for anatomical reference.

fMRI data analysis

Functional MRI data were analyzed with SPM5 (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, London, UK). To account for magnetic field equilibration, four volumes from the start of each functional run were excluded from analysis. Pre-processing of functional scans included slice time correction, within-subject registration and unwarping of time-series (to correct for motion artifacts), coregistration of the T1 image with the mean T2*-image, spatial normalization of both the functional and structural images to a standard template (Montreal Neurological Institute, MNI) and smoothing with an 8 mm Gaussian kernel. One male subject had to be excluded due to excessive head-movement during one of the runs (>4 mm), which left 23 subjects for the final analysis.

At the first level of analysis, the pre-processed functional MRI data were analyzed in the context of the general linear model (GLM) approach (Friston et al., 1995). Intrinsic autocorrelations were accounted for by 1st order auto-regression (AR(1)), and low frequency drifts were removed via high-pass filter (128 Hz). Regressors modeling the three different anticipation phases (expectation of 1 Euro, expectation of 20 cents and expectation of 0 Euro) and five different outcome phases (receipt of 1 Euro, omission of 1 Euro, receipt of 20 cents, omission of 20 cents, and receipt of 0 Euro/neutral outcome) were modeled separately as explanatory variables convolved with the gamma-variate function described by Cohen (1997). Targets and error-trials were included as additional regressors of no-interest. Linear combinations of the estimated GLM parameters allow the assessment of changes in BOLD response in the individual subjects, contingent on the experimental condition. Individual contrast images corresponding to the effects of interest were then constructed. To analyze anticipation of reward we contrasted the anticipation of a reward (1 Euro and 20 cents) with the anticipation of 0 Euro. To analyze the impact of a rewarding outcome, we followed a previous report by Ströhle et al. (2008) and contrasted the receipt of a reward (1 Euro and 20 cents) with the omission of a reward (1 Euro and 20 cents), controlling for the anticipation phase which preceded both of these outcome types.

At the second level of analysis, the individual contrast images of all subjects were included in a random effect analysis, allowing population inference (Holmes and Friston, 1998). Within-group activation was compared using a one-sample *t*-test. A whole brain analysis using the specific contrasts of interests was carried out in order to identify reward-sensitive brain areas. We report results significant at a family-wise error corrected cluster level threshold of $p < 0.05$ (cluster defining threshold $p < 0.001$ uncorrected). The location of the peak activity associated with each cluster of activation is reported in MNI-coordinates.

Correlational analysis between activity in Region of interests (ROI) and psychometric scales

In order to assess brain activation in the VS and the amygdala, we used an anatomical voxel-mask retrieved from a publication-based probabilistic MNI-atlas (Nielsen and Hansen, 2002, please refer to http://hendrix.imm.dtu.dk/services/jerne/ninf/voi/index-alphabetic.html, access date June 2008), which was used in previous studies (Juckel et al., 2006; e.g. Schlagenhauf et al., 2008). Regarding the orbitofrontal ROI, structural templates encompass rather large parts of the OFC, which subserve at least partially different functions. Therefore, we used a functional ROI based on the initial whole-brain analysis during the contrast receipt of a reward (1 Euro and 20 cents) vs. omission of a reward (1 Euro and 20 cents). The mOFC ROI was defined as the orbitofrontal voxels passing a threshold of $p < 0.001$ uncorrected. Overall, three ROIs were investigated to address brain–

Table 1
Group maximum *t*-values and MNI-coordinates of all activation foci found during expectation and outcome period.

Area	Hemi	*t*-value at peak voxel	Cluster size	MNI-coordinates		
				x	*y*	*z*
Anticipation of reward vs. non-reward						
Ventral striatum	R	5,58	72	15	3	−3
Receipt of reward vs. omission of reward						
Ventral striatum	R	8,26	1072	18	12	3
Medial orbitofrontal cortex	L/R	5,99	349	0	48	−6
Inferior temporal gyrus	L	7,34	435	−45	57	−9
Inferior temporal gyrus	R	6,78	510	48	51	−12
Medial ventral ACC	R	5,76	36	6	−3	30
Thalamus	L	5,07	40	−3	−9	9
Inferior frontal gyrus	L	5,04	87	−45	6	36
Inferior frontal gyrus	R	4,87	26	33	−3	24

Results significant at a family-wise error corrected cluster level threshold of $p<0.05$ (cluster defining threshold $p<0.001$ uncorrected).

behavior relationships: VS (structural), mOFC (functional) and amygdala (structural). For all ROIs mean percent signal change from the mean of overall intensity was extracted using MarsBaR (Brett et al., 2002). Simple correlations were performed between the BIS/BAS scales and mean percent signal change using SPSS version 13.0.

Results

Behavioral results

The average error rate of all subjects was 0.4%. Subjects were significantly faster in trials when 1 Euro was promised (mean 477 ms, SD 59 ms) than in trials where they expected no reward (mean 507 ms, SD 55 ms; $t=-4.2$, $p<0.001$), as well as in trials where they could win 20 cents as opposed to no reward (mean 490 ms, SD 51 ms; $t=-2.5$, $p=0.01$). Additionally, subjects were significantly faster during the expectation of 1 Euro in comparison to the expectation of 20 cents ($t=-3.19$, $p=0.002$).

Ratings confirmed that subjects perceived the reward cues as more arousing than the 0 Euro cue (1 Euro: $t=5.9$, $p<0.001$; 20 cents: $t=4.4$, $p<0.001$). The valence rating showed a significant difference between the 1 Euro cue and the non-rewarding cue ($t=1.8$, $p=0.038$), but no significant difference between the 20 cent cue and the non-rewarding cue ($t=0.6$, $p=0.27$).

Neural activity during anticipation of reward

The analyses for the contrast "anticipation of reward (1 Euro and 20 cents) versus anticipation of no reward" revealed increased activation in the right ventral striatum including the nucleus accumbens.

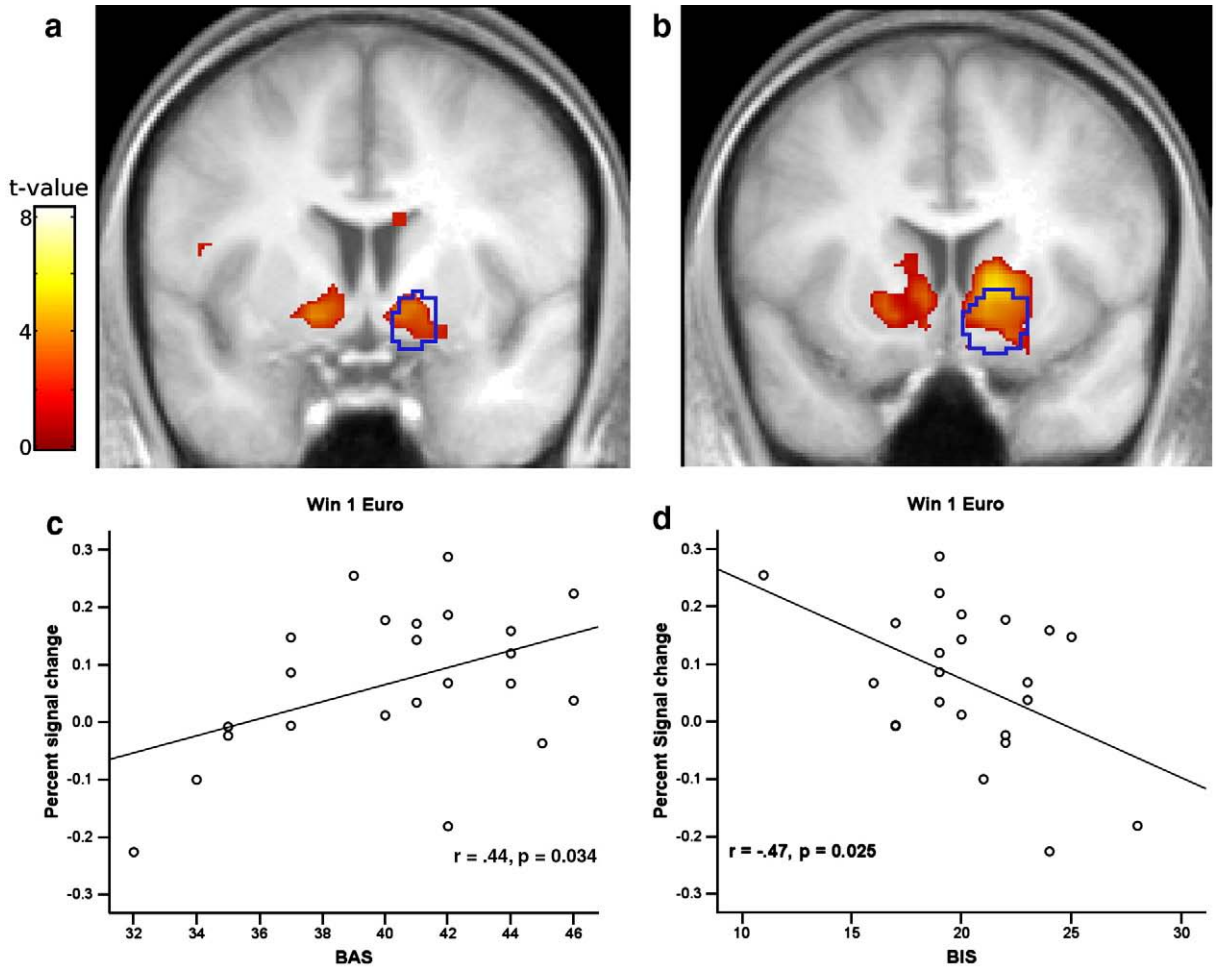

Fig. 2. Activation in the ventral striatum during the expectation of 1 Euro compared to the expectation of 0 Euro (a) and during receipt of 1 Euro compared to the omission 1 Euro (b). The threshold is set at $p<0.001$ uncorrected, *t*-maps are overlaid on a normalized structural image averaged across all subjects. The shape of the structurally defined ROI for correlation analyses is overlaid on the functional image, depicted with a blue line. Correlation between percent signal change from baseline in the right ventral striatum averaged over trials, during the receipt of 1 Euro and the BAS scale (c) and between percent signal change during the receipt of 1 Euro and the BIS scale (d).

Table 2
Group maximum *t*-values and MNI-coordinates of all activation foci found during expectation period separately for the 1 Euro and 20 cent condition.

Area	Hemi	*t*-value at peak voxel	Cluster size	MNI-coordinates		
				x	*y*	*z*
Anticipation of 1 Euro vs. non-reward						
Ventral striatum	R	6,25	199	15	0	−3
Rostral ventral ACC	L	8,28	131	−3	30	15
Anterior insula	R	5,59	68	33	18	−9
Frontal operculum	L	5,15	63	−42	9	12
Medial ventral ACC	L/R	4,77	51	0	12	24
Thalamus	L	4,21	44	−6	−27	0
Anticipation of 20 cents vs. non-reward						
–	–	–	–	–	–	–

Results significant at a family-wise error corrected cluster level threshold of $p<0.05$ (cluster defining threshold $p<0.001$ uncorrected).

Neural activity during receipt of reward

Results for the whole-brain analysis are given in Table 1. The analyses for the contrast "receipt of reward (1 Euro and 20 cents) versus omission of reward" revealed increased activation in the medial orbitofrontal cortex, but also in the right ventral striatum, including the nucleus accumbens. Additional activated areas were found in the bilateral inferior temporal gyrus, ventral cingulate gyrus, thalamus, and inferior frontal gyrus (cf. Table 1).

Analysis of inter-individual differences in neural activity

A whole brain analysis of the contrast "expectation of 1 Euro vs. expectation of 0 Euro" revealed significant activation of striatal regions (Fig. 2a, for additional regions, see Table 2), which was not the case for the contrast "expectation of 20 cents vs. expectation of 0 Euro" (Table 2). However, during the outcome phase, both the 1 Euro condition and 20 cent condition elicited similar activation patterns in comparison to the 0 Euro condition. A paired samples *t*-test comparing signal change assessed in the VS during the expectation of 1 Euro and signal change assessed during the expectation of 20 cents revealed a significant difference ($p=0.006$, $t=3$). In conjunction with the behavioral reactions and ratings in response to the incentive cues, we concluded that the 20 cent condition did not elicit a strong enough incentive strength. We therefore excluded the 20 cent condition from further analysis. As expectation- and reward-related activations were most prominent in the right VS, correlation analyses are reported for the right VS.

Correlations between behavioral approach and neural activity

We observed no significant correlations between percent signal change and BAS during the expectation of a reward. In contrast, there was a positive correlation between BAS and VS activity during the receipt of 1 Euro ($r=.44$, $p=0.034$) (see Fig. 2c). For the mOFC, we found positive correlations between the BAS and different types of

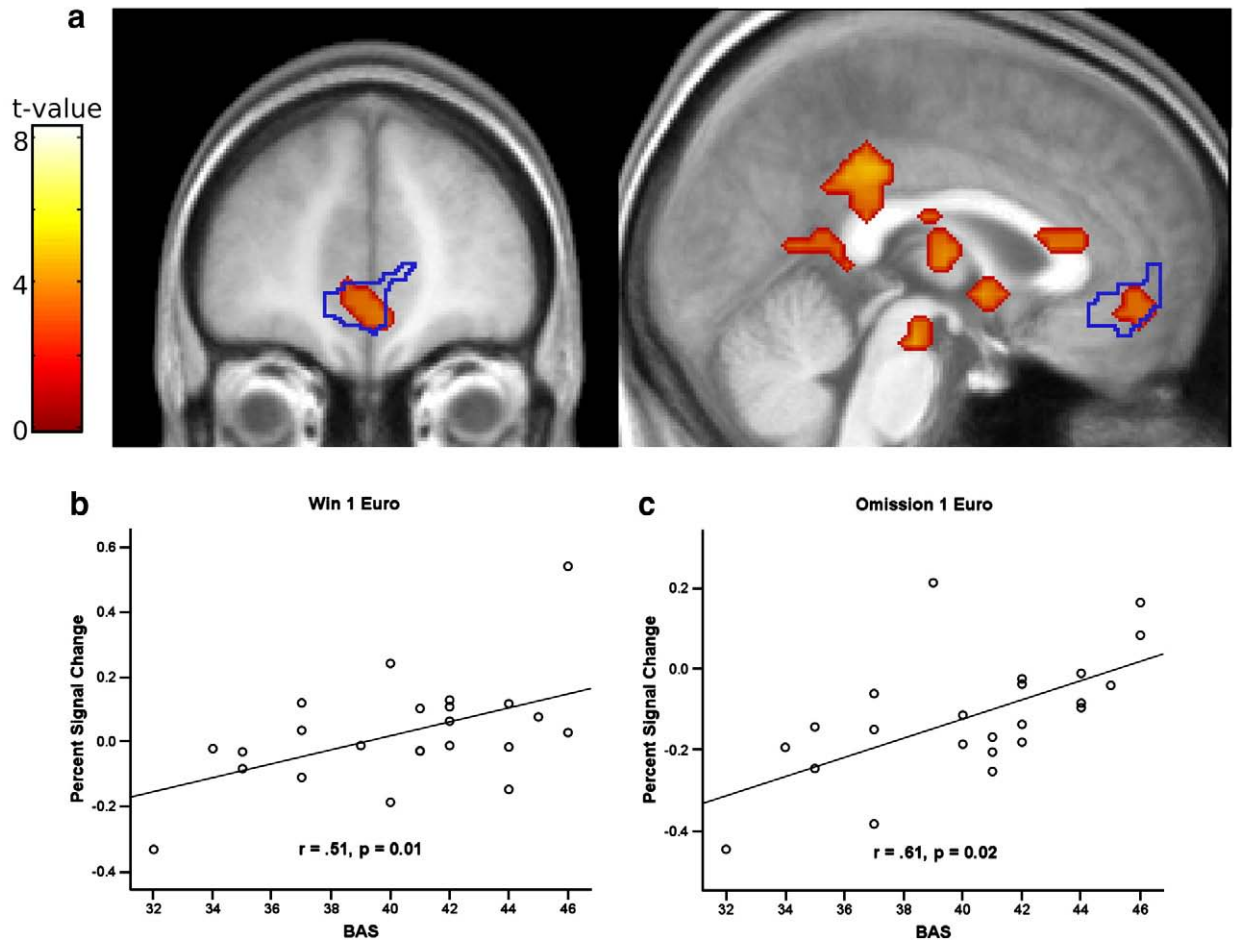

Fig. 3. Activation in the medial orbitofrontal cortex during receipt of 1 Euro compared to the omission of 1 Euro (a). The threshold is set at $p<0.001$ uncorrected, *t*-maps are overlaid on a normalized structural image averaged across all subjects. The functional ROI has been outlined with a blue line and consists of orbitofrontal voxels significant at the $p<0.001$ level in the "receipt of a reward (1 Euro and 20 cents) vs. omission of a reward (1 Euro and 20 cents)" contrast. Correlation between percent signal change from baseline in the medial orbitofrontal cortex averaged over trials and the BAS scale during receipt of 1 Euro (c), and omission of 1 Euro (d).

outcomes. More specifically, there were correlations with the receipt of 1 Euro ($r = .51$, $p = 0.01$) as well as with the omission of 1 Euro ($r = .61$, $p = 0.02$) (Fig. 3). The distribution of the data points revealed a noticeable outlier in the correlation between BAS and receipt of 1 Euro (see Fig. 3b). However, the exclusion of the respective subject still led to a significant result ($r = .42$, $p = 0.05$).

Correlations between behavioral inhibition and neural activity

We observed a negative correlation of the BIS with VS activation during the receipt of 1 Euro ($r = -.47$, $p = 0.025$), a finding which was characterized by an outlier. The exclusion of this subject led to a trend wise significant results ($r = -.37$, $p = 0.088$) (see Fig. 2d). There were no significant correlations between the BIS and activity in the amygdala and mOFC during expectation, receipt and omission of a reward.

Discussion

The main goal of this study was to investigate the relationship between personality traits and neural reward processing in healthy subjects. We used a monetary incentive delay task as a neural probe in order to display reward-related processing using fMRI. We observed a significant activation in the VS during the expectation of a possible reward, and a significant activation of the mOFC during the receipt of a reward. These activations are in line with findings from prior studies investigating the neural correlates of reward processing (e.g. Abler et al., 2005; Knutson et al., 2003). Additionally, we found a strong VS response during the receipt of a reward, an observation made in some (Bjork et al., 2004; Dillon et al., 2008), but not all previous studies (Knutson et al., 2003). This is most parsimoniously explained in terms of prediction error signaling, because we used a probabilistic reward pattern in which rewarded outcomes are better than the prediction and non-rewarded outcomes worse than the prediction (Berns et al., 2001). These robust findings provide the basis for the analysis of personality effects on the neural processing of reward.

In line with our predictions, subjects with high BAS showed a stronger activation in the VS during the receipt of a reward, indicating an elevated reactivity to rewarding outcomes. Furthermore, a high BAS led to higher activation of the mOFC during rewarding outcomes and less deactivation during the omission of a reward. The modulation of the VS response to monetary rewards suggests that in subjects with high BAS, a monetary reward exerts a stronger saliency (Jensen et al., 2007). In addition, they display a reduced reactivity to negative outcomes. Although deactivations are generally difficult to interpret, this could indicate a reduced amount of negative emotions in response to displeasing outcomes (Knutson et al., 2003; Kringelbach et al., 2003). A higher, valence-independent DA signaling from limbic regions to the OFC could be considered a possible explanation for this observation, since the BAS is assumed to rely mainly on DA projections (Pickering and Gray, 2001).

Our results partially fit to recent investigations of reward-related neural processing in subjects suffering from ADHD (Scheres et al., 2007; Ströhle et al., 2008), which found an attenuated effect of reward expectation and an increased effect of rewarding outcomes. This disorder has indeed been conceptualized as resulting from an overactive BAS, which results in an overresponsiveness to rewarding stimuli (Mitchell and Nelson-Gray, 2006). Although we did not observe reduced striatal activity during expectation, we found that a high BAS produces a higher responsiveness to the receipt of a reward in both the VS and mOFC, thus extending findings from ADHD to individual differences in BAS reactivity in the normal range.

As expected, a low BAS was related to reduced activity during the receipt of a reward in the VS and to less activity of the mOFC during positive outcomes as well as a stronger deactivation during the omission of 1 Euro. This finding points to a lower hedonic reactivity to rewards and adds further background to the often made association between a low approach motivation and depression. Our results are in line with the observation of impaired neural processing of rewarding outcomes in patients with depression (Steele et al., 2007). The association with decreased responses to rewards can be linked to anhedonia, i.e., loss of pleasure which is a prominent symptom of depression. Interestingly, recent concepts of depression have also implicated the dopaminergic reward system in addition to the more "classical" serotonergic and noradrenergic dysfunctions (Nestler and Carlezon, 2006).

The lack of correlations between BIS scores and activity in the amygdala in the present paradigm might be a result of our use of a simple and non-aversive task which led to low pressure of performance. In addition, it is noteworthy that recent studies have begun to criticize the assumed connection between the amygdala and the BIS, calling for a re-examination of the specific neural substrates of the BIS (Cherbuin et al., 2008; Morgan, 2006). Here, we demonstrate that a high BIS leads to less activation in the VS during the receipt of a reward. This indicates that although the behavioral inhibition system might rely on neural substrates outside the dopaminergic reward system, there is also a direct attenuating influence on the mesolimbic reward circuitry.

In summary, the observed activity in the mOFC indicates that subjects with high BAS show an increased hedonic response to rewarding outcomes, and their neural reward processing is modulated to a lesser extent by the omission of a positive outcome. Subjects with high BIS show less activity during the receipt of a reward. An overall tendency for anxiety as reflected by high BIS scores seems to abate physiological reactivity to rewards. In contrast, impulsiveness as reflected by higher BAS scores leads to an increase in activity of the mesolimbic-mesocortical reward system during an incentive task. Additionally, the connection between low BAS and depression might be due to the observed relation with the reward system. To conclude, the spectrum of approach- and avoidance-related behavioral tendencies tested here is implicated in several psychiatric disorders, but also relevant in normal, non-pathological responses to reward and reward anticipation. For this reason, personality differences should be taken into account when investigating the neural processing of reward. The present study furthermore contributes to the neurobiological foundation of Reinforcement Sensitivity Theory by giving additional support to the assumption that individual differences in approach and avoidance tendencies can indeed be measured on a neural level of appetitive functioning.

Acknowledgments

JJS is supported by a postgraduate fellowship provided by the State of Baden-Württemberg. CJF is supported by an Emmy Noether grant of the German Research Foundation (DFG FI 848/3-1) and by the Germany Excellence Initiative.

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Schizophrenia Research xxx (2009) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Neural correlates of reward processing in schizophrenia — Relationship to apathy and depression

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ARTICLE INFO

Article history:
Received 14 July 2009
Received in revised form 3 November 2009
Accepted 15 November 2009
Available online xxxx

Keywords:
Schizophrenia
Reward
fMRI
Apathy
Anhedonia
Depression

ABSTRACT

The present study employs a new framework to categorise the heterogeneous findings on the relationship between impaired reward processing and negative and affective symptoms of schizophrenia. Based on previous behavioural and neuroimaging studies we postulate that "wanting" (i.e. anticipation) of a reward is specifically related to apathy, whereas "liking" (i.e. hedonic impact) is related to anhedonia and depression — symptoms commonly observed in schizophrenia. Fifteen patients with schizophrenia or schizoaffective disorder treated with atypical antipsychotic drugs and fifteen healthy controls performed a probabilistic monetary incentive delay task while undergoing functional magnetic resonance imaging. At the group level we found no significant differences between patients and controls in neural activation during anticipation or receipt of a reward. However, in patients with schizophrenia specific relationships between ventral–striatal activation and symptoms were observed. Ventral–striatal activation during reward anticipation was negatively correlated with apathy, while activation during receipt of reward was negatively correlated with severity of depressive symptoms. These results suggest that the link between negative symptoms and reward anticipation might specifically relate to apathy, i.e. a lack of motivation and drive. Impaired hedonic reward processing might contribute to the development of depressive symptoms in patients with schizophrenia, but it is not directly associated with self-rated anhedonia. These results indicate the necessity of more specifically differentiating negative and affective symptoms in schizophrenia in order to understand the role of the reward system in their pathogenesis.

1. Introduction

The mesolimbic dopamine system is crucial for the processing of reward-related information and appears to be dysfunctional in patients with schizophrenia (Abi-Dargham et al., 2000). The importance of this system in the pathophysiology of schizophrenia has been highlighted in recent studies investigating the relationship between the neural processing of rewards and schizophrenic symptoms (Juckel et al., 2006b; Waltz et al., 2008).

More specifically, the "wanting" of a reward, which arises from its motivational incentive value (Berridge and Robinson, 1998), appears to be directly impaired in schizophrenia. Both unmedicated patients with schizophrenia and those treated with typical antipsychotics show reduced activation of the ventral striatum (VS) during reward anticipation (Juckel et al., 2006a; Kirsch et al., 2007; Schlagenhauf et al., 2008). Furthermore, a negative correlation has been found between VS activation and overall negative symptoms in unmedicated patients with schizophrenia (Juckel et al., 2006b).

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doi:10.1016/j.schres.2009.11.007

Group differences in brain activation during the receipt of a reward (i.e., "liking") have received less attention than differences arising during reward anticipation. One study compared patients treated with typical and atypical antipsychotics and found no differences during the processing of a rewarding outcome (Kirsch et al., 2007). In contrast, a further study demonstrated that higher delusional symptoms were associated with smaller medial-prefrontal-activation differences between successful and unsuccessful loss-avoidance in unmedicated patients with schizophrenia (Schlagenhauf et al., 2009).

The nature of the impairment in different stages of neural reward processing and the relationship between these stages and the negative symptoms observed in schizophrenia (e.g.: anhedonia, apathy) are thus subject to continued debate. Here, we propose a simple framework which integrates the heterogeneous findings on reward-processing impairments in schizophrenia by relating specific aspects of negative symptoms to different stages of reward processing and the corresponding structures of the dopaminergic reward system (Fig. 1).

Reward anticipation or the "wanting" of a reward has been associated with motivational processes which promote goal-directed behaviours that aim to achieve desired rewards (Schultz, 2002). Apathy or a loss of motivation, which leads to the reduction of goal-directed behaviours (Marin, 1991), may be specifically related to deficits at this stage of reward processing. Apathy is considered to be a common but treatment-resistant symptom (Buckley and Stahl, 2007) and has been conceptualised as a lack of responsiveness to stimuli and self-initiated action (Stuss et al., 2000). This symptom might therefore be a direct consequence of the diminished activation of the VS observed in patients with schizophrenia during anticipation (Fig. 1a).

The hedonic impact or the "liking" of a reward has been linked to activity in prefrontal areas and specifically to the medial orbitofrontal cortex (mOFC) (Kringelbach, 2005), whereas the VS codes positive prediction errors in response to unexpected rewards (Berns et al., 2001). Impaired neural processing during this stage of reward processing may be independent from motivational components given that hedonic impact has been found to be independent from anticipation effects (Gard et al., 2007; Kring and Neale, 1996). Anhedonia and depression represent common yet distinct symptoms of schizophrenia and are both negatively related to experiences of positive emotions in daily life (Horan et al., 2006; Pizzagalli et al., 2005; Siris, 2000). Both symptoms are additionally characterised by an altered reward circuitry (Holcomb and Rowland, 2007; Martin-Soelch, 2009). Consequently, blunted responses to rewarding outcomes may be related to these symptoms (Fig. 1b).

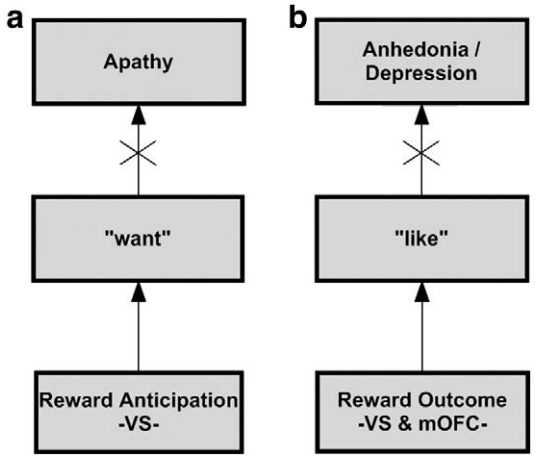

Fig. 1. Schematic depiction of hypotheses. (a) Dysfunctional activation of the ventral striatum (VS) observed during anticipation of reward leads to apathy. (b) Dysfunctional activation of the VS and/or the medial orbitofrontal cortex (mOFC) during receipt of reward leads to symptoms of anhedonia and/or depression.

In the present study, we compared the neural activation of healthy controls and patients with schizophrenia treated with atypical neuroleptics during both reward anticipation and outcome. Our main goal was to relate specific symptoms of schizophrenia – notably apathy, anhedonia, and depression – to changes in neural activity during the different stages of reward processing.

2. Methods

2.1. Participants

We included 15 right-handed healthy controls and 15 right-handed patients with schizophrenia or schizoaffective disorder. Patients with schizophrenia were recruited at the Psychiatric Hospital of the University of Heidelberg. A structured clinical interview for DSM-IV, the MINI (Sheehan et al., 1998), was employed to confirm diagnoses and to rule out both other DSM Axis I disorders and current drug abuse. All patients were medicated with atypical antipsychotics (four clozapine, three risperidone, two aripiprazole, two olanzapine, one quetiapine, one amisulpride, one risperidone and quetiapine, one clozapine and amisulpride). Five patients were additionally treated with an antidepressant or a mood-stabilizer (three escitalopram, one lithium, one lamotrigine). Control participants were screened for neurological or psychiatric disorders using the Symptom Checklist-90-Revised (Schmitz et al., 2000). The present study complies with the Code of Ethics of the World Medical Association (Declaration of Helsinki, version 2004) and was approved by the Ethics Committee of the Medical School of the University of Heidelberg. All participants provided their written informed consent following a full explanation of the procedures.

2.2. Clinical and psychometric scales

In patients with schizophrenia, psychopathological symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987), a German version of the Calgary Depression Scale for Schizophrenia (CDSS-G; Müller et al., 1999), and a German version of the Apathy Evaluation Scale (AES-D; Lueken et al., 2006). In order to assess anhedonic symptoms, a German version of the Chapman scales for physical and social anhedonia (PAS, SAS; Burgdörfer and Hautzinger, 1987; Scherbarth-Roschmann and Hautzinger, 1991) was administered to both healthy controls and patients.

Please cite this article as: Simon, J.J., et al., Neural correlates of reward processing in schizophrenia — Relationship to apathy and depression, Schizophr. Res. (2009), doi:10.1016/j.schres.2009.11.007

2.3. Monetary incentive delay task

We employed a modified version of the "monetary incentive delay task", as proposed by Abler and colleagues (Fig. 2, Abler et al., 2005; Knutson et al., 2001). Before entering the scanner, the experimental procedure and the task were explained to the participants and they were shown the money (up to 36 euro) which they could earn by performing the task successfully. Participants engaged in two 11-minute sessions, each of which comprised 70 trials of the task. Functional images were recorded throughout the task.

Each trial commenced with the presentation of a symbol ("cue", 750 ms) indicating the amount of money which participants could win (i.e., 1 euro, 20 cents, or 0 euro) by responding correctly. Following an anticipation period ("delay", 3000 ms), participants were required to correctly react to one of two symbols ("targets"; i.e., a triangle inclined to the right or the left) with a left or right button press according to the direction of the triangle (index or middle finger) within a fixed interval of 1 s. Employing a fixed response-time-frame results in a low task difficulty and a very high success rate. In order to guarantee a steady rate of reward *vs.* non-reward across all participants, we applied a probabilistic reward pattern which entailed no reward being paid out in 40 predefined trials (out of the 100 trials with a potential reward). This procedure allows reaction times to be used as a measure of motivation (Abler et al., 2007). Feedback was provided immediately following target presentation ("feedback", 1500 ms) and notified participants about the amount of money they had won as well as their cumulative total. Incorrect button presses resulted in an outcome of 0 euro. To ensure that participants responded in all experimental conditions, a penalty of −1 euro was applied whenever no button press occurred in a trial.

In order to increase statistical efficiency, trials were separated by jittered intertrial intervals (ITIs) which ranged from 1 to 8 s, with a mean duration of 3.5 s (Dale, 1999). After exiting the scanner, participants retrospectively rated how they felt when viewing each of the 3 cues and 2 targets on the dimensions valence and arousal, using a nine-point self-assessment manikin (SAM; Bradley and Lang (1994).

2.4. Magnetic resonance imaging acquisition

Images were collected using a 3-Tesla Siemens Trio magnetic resonance imaging (MRI) scanner (Siemens Medical Solutions, Erlangen, Germany) equipped with a standard single-channel head coil. Participants performed two functional runs, each lasting 12 min with 347 volumes. In order to minimise susceptibility artefacts in the orbitofrontal cortex, 33 oblique slices with a 45-degree angle relative to the anterior–posterior-commissure (AC–PC) axis were acquired with the following parameters: TR = 2000 ms, TE = 30 ms, resulting in an in-plane resolution of $3 \times 3 \times 3$ mm^3, flip angle = 80°, field of view = 192×192 mm. Participants viewed visual stimuli on a projection screen via a mirror fixed to the head coil and responded with the right hand using a button box. Following the functional scans, high-resolution T1 MPRAGE anatomical images were acquired (176 slices, voxel size $1 \times 1 \times 1$ mm, TR 11 ms, TE 4.92 ms, 15° flip angle) for anatomical reference.

2.5. Image processing

Functional MRI data were analysed using SPM5 (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, London, UK). Pre-processing of functional scans included slice-time correction, within-subject registration and unwarping of time series (to correct for motion artefacts), co-registration of the T1 image with the mean T2*-image, spatial normalisation of both the functional and structural images to a

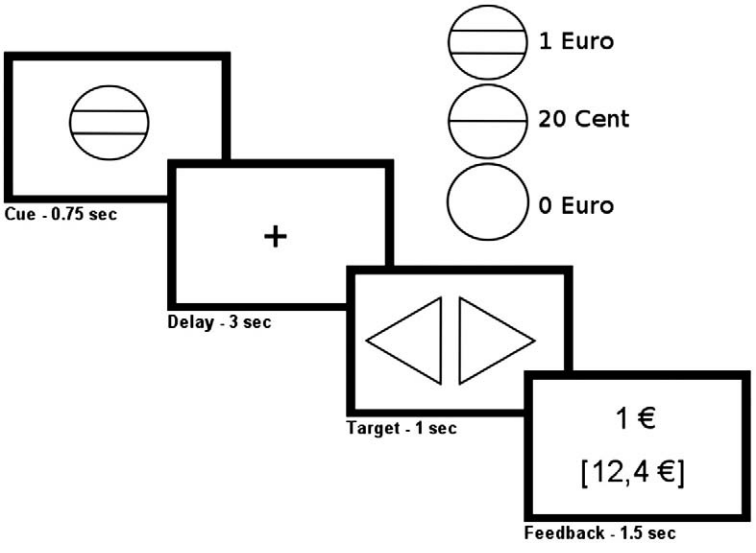

Fig. 2. Cues representing possible reward outcomes (1 euro, 20 cents and 0 euro) and task structure of the monetary incentive delay task. Participants were first presented with a cue stipulating the amount of money they could win if they reacted correctly during the ensuing discrimination task. Immediately after target presentation, participants were informed about the amount of money they had won during the trial and were presented with their cumulative total win so far (Abler et al., 2005).

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standard template (Montreal Neurological Institute, MNI), and smoothing with an 8 mm Gaussian kernel.

At the first level of analysis, pre-processed functional MRI data were analysed in the context of the general linear model (GLM) approach (Friston et al., 1995). Regressors were modelled separately for the three different anticipation phases (anticipation of 1 euro, anticipation of 20 cents, and anticipation of 0 euro) and the five different outcome phases (receipt of 1 euro, omission of 1 euro, receipt of 20 cents, omission of 20 cents, and receipt of 0 euro/neutral outcome) as explanatory variables convolved with the gamma-variate function described by Cohen (1997). Targets and error trials were included as additional regressors of no interest. Linear combinations of the estimated GLM parameters allow the assessment of changes in the BOLD responses of individual participants, contingent on the experimental condition. Individual contrast images corresponding to the effects of interest were subsequently constructed. The analysis of reward anticipation involved contrasting the anticipation of a reward (1 euro and 20 cents) with the anticipation of 0 euro. For analysis of the impact of a rewarding outcome, we contrasted the receipt of a reward (1 euro and 20 cents) with the omission of a reward (1 euro and 20 cents), controlling for the anticipation phase which preceded both outcome types. This procedure is in line with a previous report by Ströhle et al. (2008).

At the second level of analysis, the individual contrast images of all participants were included in a random-effects analysis; within-group activation was compared using a one-sample *t*-test and between-group activation using a two-sample *t*-test.

2.6. Region-of-interest definition and correlation analysis

In order to assess brain activation in the VS, we used an anatomical voxel-mask taken from a publication-based probabilistic Montreal Neurological Institute (MNI) atlas (Nielsen and Hansen, 2002, please refer to http://hendrix.imm.dtu.dk/services/jerne/ninf/voi/index-alphabetic.html, access date June 2008), which has been used in previous studies (Fig. 3a and b, Juckel et al., 2006b; Schlagenhauf et al., 2008). With regard to the orbitofrontal region of interest

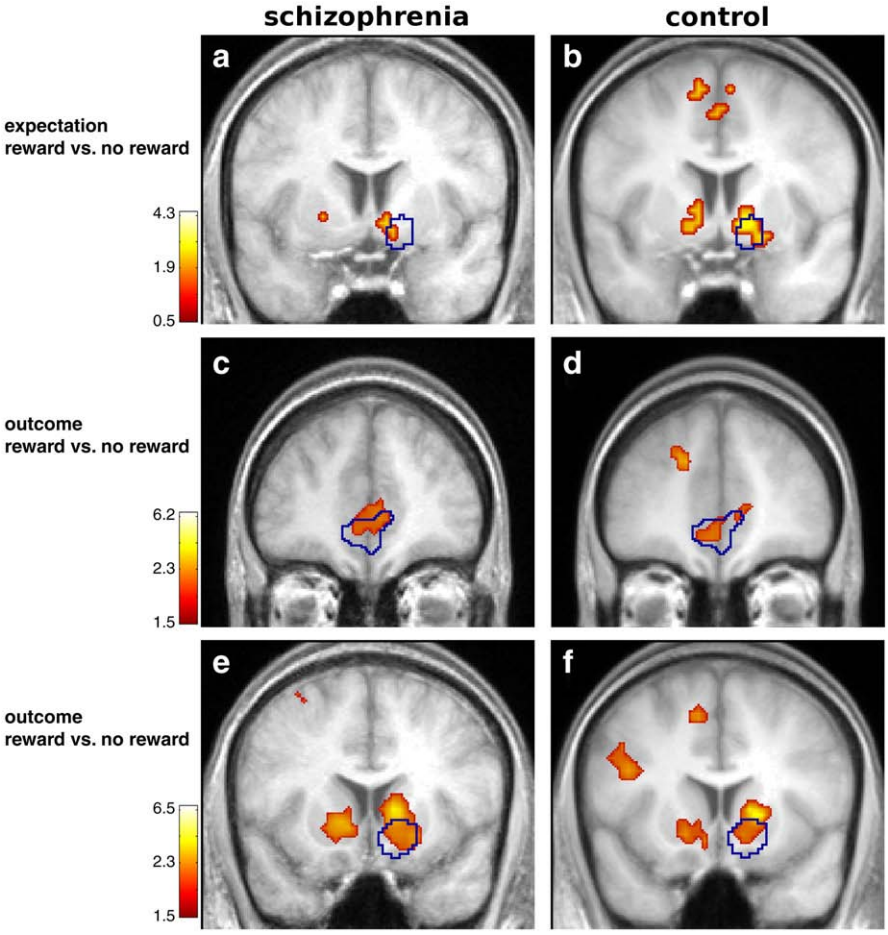

Fig. 3. Within-group activation maps of the contrasts *reward anticipation vs. no reward anticipation* for patients with schizophrenia (a) and healthy controls (b) as well as *receipt of reward vs. omission of a reward* for patients with schizophrenia (c, e) and healthy controls (d, f). The threshold was set at $p<0.005$ uncorrected with a cluster-defining threshold of 10 voxels for illustrative purposes. T-maps for both groups were overlaid on a normalised structural image averaged across all participants in the respective group. The VS and mOFC ROIs are outlined in blue. The VS ROI was defined structurally whereas the mOFC ROI was defined functionally and based on the contrast between *receipt of reward vs. omission of reward* performed in a previous study with healthy participants (Simon et al., in press). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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(ROI), structural templates encompass rather large parts of the OFC which subserve at least partially different functions. We therefore used a functional ROI based on the initial whole-brain analysis of a previous study (Simon et al., in press) which employed the same paradigm in a sample of healthy participants ($N=23$) and contrasted the receipt with the omission of a reward. The mOFC ROI was defined as the orbitofrontal voxels passing a threshold of $p<0.001$ uncorrected (Fig. 3c and d). Mean percent signal change was extracted for the VS and mOFC ROIs using MarsBaR (Brett et al., 2002). Simple correlation analyses were performed for psychopathological ratings (i.e., PANSS Negative and PANSS Positive, PAS/SAS, AESd, CDSS-G) and mean percent signal change in the VS and mOFC using SPSS version 13.0.

3. Results

3.1. Demographic, clinical and behavioural data

Demographic, clinical and behavioural data are summarised in Table 1. There were no significant group differences with respect to age, education, reaction times, or the total amount of money earned. Patients with schizophrenia rated the reward cues and targets as more arousing than healthy controls (reward cues $t=2.5$, $p=0.018$, targets $t=2.1$, $p=0.041$) and displayed greater physical-anhedonia scores ($t=2.36$, $p=0.013$).

3.2. fMRI data

In order to identify significant activations in the contrasts of interest for both groups, we calculated paired *t*-tests for the VS and mOFC ROI using MarsBaR. In the contrast *reward anticipation vs. no reward anticipation*, both healthy controls and patients showed significant activations in the VS ($t=3.06$, $p=0.0042$ and $t=2.21$, $p=0.022$, respectively). Similarly, in the contrast *receipt of reward vs. omission of reward*, significant activations were observed for both groups in the VS ($t=3.65$, $p=0.001$ and $t=4.08$, $p=0.0005$, respectively) and mOFC ($t=3.32$, $p=0.002$ and $t=2.67$, $p=0.009$, respectively).

Table 1
Demographic, clinical and behavioural data[a].

	Healthy controls	Patients with schizophrenia
Age (years)	25.2 ± 3.2 (20–32)	26.3 ± 5.4 (18–38)
Gender	5 females, 10 males	5 females, 10 males
Education (years)	13.3 ± 2.9	12.8 ± 2
Duration of illness (years)		5.8 ± 4.8
Age of onset (years)		20.8 ± 3.6
PAS	6.2 ± 4.4 (0–15)	11.3 ± 7 (3–24)
SAS	10 ± 4.8 (3–19)	7.8 ± 5.1 (2–17)
PANSS general		30.6 ± 4.4 (26–45)
PANSS positive		11.3 ± 2.1 (7–15)
PANSS negative		18.1 ± 4.5 (11–27)
AESd		47.9 ± 8.7 (25–60)
CDSS-G		4.6 ± 3.1 (0–11)
Reaction time (ms)	486 ± 54.5	498 ± 70.1
Total gain (in euro)	34.3 ± 2.97	34.7 ± 1.71
Arousal rating reward cues	4.8 ± 1.6 (1–7)	6.2 ± 1.2 (4–8)
Valence rating reward cues	6 ± 1.5 (3.5–8)	6.2 ± 1.5 (3–9)

[a] Values given as mean ± SD (minimum–maximum).

A comparison of the activation in ROIs between healthy controls and patients revealed no significant differences in the contrasts *reward anticipation vs. no reward anticipation* or *receipt of reward vs. omission of reward*. Similarly, an ANOVA with repeated measures revealed no group differences in signal changes in the VS or mOFC ROIs for regressors of interest relative to baseline.

3.3. Correlations with symptoms during anticipation of reward — "wanting"

We found a significant negative correlation between activation in the VS during reward anticipation and the Apathy Evaluation Scale (AES, $r=-0.58$, $p=0.02$) for patients with schizophrenia. The graphic depiction of the correlation reveals one outlier (Fig. 4a). However, a trend-level effect ($r=-0.49$, $p=0.07$) was still found when

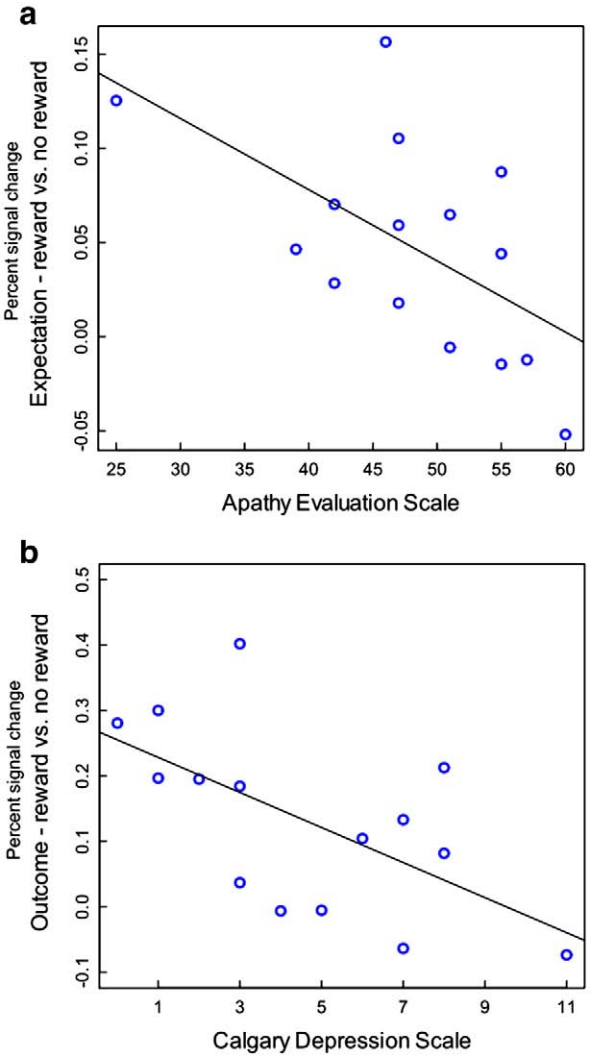

Fig. 4. (a) Correlation between percent signal change in the right VS during anticipation of a reward (1 euro and 20 cents) and apathy scores ($r=-0.58$, $p=0.02$). (b) Correlation between percent signal change in the right VS during receipt of a reward (1 euro and 20 cents) and depression scores ($r=-0.61$, $p=0.016$).

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performing the same analysis with exclusion of the respective participant. In contrast, we observed no relationship between signal change assessed in the VS during reward anticipation (1 euro and 20 cents) and overall negative symptoms measured using the PANSS negative subscale.

3.4. Correlations with symptoms during receipt of reward — "liking"

A significant correlation was found between VS activation in patients with schizophrenia during the receipt of a reward (1 euro and 20 cents) and depression severity rated using the CDSS-G ($r = -0.61$, $p = 0.016$, Fig. 4b) but not with anhedonia measured using the Chapman scales. No significant associations were found between mOFC signal change and psychopathological ratings. There were also no significant correlations between the physical and social anhedonia scores and mean percent signal change in healthy controls.

4. Discussion

We found that patients with schizophrenia treated with atypical antipsychotic drugs performed as well as healthy controls during the monetary incentive delay task. At the group level there were no significant differences between patients and controls in neural activation during anticipation or receipt of a reward. These observations correspond with most (Juckel et al., 2006a; Kirsch et al., 2007; Schlagenhauf et al., 2008) but not all previous studies (Waltz et al., 2008). More importantly and in line with our assumptions, the neural processing of both anticipation and receipt of reward was specifically related to the assessed symptoms of schizophrenia.

Patients with higher apathy scores showed lower activation of the VS during reward anticipation. However, there was no such relationship with the PANSS subscale for negative symptoms, which is consistent with a previous study in patients treated with olanzapine (Schlagenhauf et al., 2008). This suggests that apathy might be more specifically related to reward anticipation than overall negative symptoms. Apathy is found in diseases with dysfunctional dopamine transmission in the reward circuit (Bressan and Crippa, 2005), such as neurodegenerative disorders (Kirsch-Darrow et al., 2006; Marshall et al., 2007) and focal lesions of the basal ganglia (Bhatia and Marsden, 1994). This has led to the hypothesis that apathy may partly be explained by dysfunctional basal-ganglia activity (Levy and Czernecki, 2006). Striatal dopamine D2 receptor availability has been observed to be directly related to apathy severity in patients with schizophrenia (Heinz et al., 1998). Among negative symptoms, apathy might thus be a key manifestation of dysfunctional VS activity during reward processing. This indicates the need for a clear differentiation of the diverse components of negative symptoms in order to understand the role of the reward system in their pathogenesis.

We observed a negative relationship between severity of depressive symptoms and VS activation during the receipt of reward. This result is consistent with findings of decreased striatal response to positive feedback in patients with major depression (Steele et al., 2007). The neural coding of pleasurable experiences in the ventral striatum may contribute to the neurobiological origin of depression in the context of schizophrenia. In contrast, while patients with schizophrenia attained higher physical-anhedonia scores, the hypothesised relationship between anhedonia and the neural coding of rewarding outcomes was not confirmed. This may indicate that the assessed symptoms of anhedonia in patients with schizophrenia are not directly related to the impaired experience of pleasurable events. Activity in the mOFC during the receipt of a reward was not related to anhedonia scores, although it has been proposed to reflect coding of the reward's hedonic impact (Kringelbach, 2005). While the mOFC is involved in the coding of immediate and simple hedonic responses, the employed anhedonia scales primarily assess "trait"-like aspects which relate to more complex situations. Activity in the mOFC and the scales measuring anhedonia may thus be related to concepts which partially differ, explaining why the two are not directly associated. In contrast, our findings suggest that neural processing of rewarding outcomes in the VS might be strongly linked to depressive symptoms in patients with schizophrenia.

Previous studies have also suggested a close link between depression and blunted hedonic capacity (Loas, 1996; Sloan et al., 2001). It is important to note that the self-report questionnaire used to assess anhedonia in the present study is potentially limited by the patient's ability to recall and relate to particular experiences (Horan et al., 2006). Furthermore, the Chapman anhedonia scales do not distinguish between anticipatory and consummatory aspects of anhedonia which may limit assessment of these symptoms. A new scale developed by Gard et al. – the Temporal Experience of Pleasure Scale (TEPS) (Gard et al., 2006) – specifically addresses these two distinct aspects. It is unfortunately not yet available in German and therefore could not be used in the present study. The notion that anhedonia in schizophrenia is not directly linked to hedonic processing but may rather be secondary to motivational deficits has begun to emerge in the recent literature (Wolf, 2006). Foussias and Remington have argued that avolition accounts for reductions in goal-directed behaviour and functional performance, which are misinterpreted as a deficit in hedonic capacity (Foussias and Remington, 2008).

In a review of their own research activities, Gold et al. conclude that the failure to observe significant correlations between negative symptoms and reward processing might be due to three reasons: 1) imprecise assessment of negative symptoms, 2) medication, and 3) the failure to identify specific dimensions of reward processing which might be linked to negative symptoms (Gold et al., 2008). In light of these considerations and our own data, we propose that apathy might be triggered by deficits in anticipatory reward processing, whereas depressive symptoms might be specifically related to impaired responses to rewarding outcomes in patients with schizophrenia. The heterogeneous medication received by patients represents a potential limitation of this study, although our findings are in line with previous research in patients treated with atypical antipsychotics. In addition, we predominantly focused on within-group correlations and did not rely on the comparison between medicated patients and unmedicated controls. Nonetheless, antipsychotic drugs may also modulate the relationship between symptom dimensions and brain activation in patients with schizophrenia. To our knowledge, these potential modulatory effects have so far not

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been systematically addressed and represent an important issue for further research. Overall, our findings indicate that a differentiation of common negative and depressive symptoms in schizophrenia might be important for understanding their relationship with dysfunctional reward processing.

Role of funding source

Joe J. Simon is supported by a doctoral scholarship from the state of Baden-Wuerttemberg through the Landesgraduiertenförderung (LGFG). The LGFG had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Contributors

Joe Simon and Stefan Kaiser designed the study and wrote the protocol. Matthias Weisbrod and Daniela Roesch-Ely reviewed the protocol and contributed to the analytic approach. Joe Simon, Stephan Walther and Armin Biller collected the data. Joe Simon, Stephan Walther, Christoph Stippich and Armin Biller undertook the statistical analyses and prepared them for presentation. Joe Simon and Stefan Kaiser wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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Please cite this article as: Simon, J.J., et al., Neural correlates of reward processing in schizophrenia — Relationship to apathy and depression, Schizophr. Res. (2009), doi:10.1016/j.schres.2009.11.007

Brief Report

Motor impulsivity and the ventrolateral prefrontal cortex

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Abstract

Functional magnetic resonance imaging in a Go/Nogo task was employed to investigate the relationship between trait impulsivity and brain activation during motor response inhibition. We found a positive correlation between motor impulsivity and activation of bilateral ventrolateral prefrontal cortex during successful inhibitions, which suggests stronger recruitment to maintain task performance.

Keywords: functional magnetic resonance imaging, go/nogo, barratt impulsiveness scale

1. Introduction

Impulsivity has been defined as behavior that is poorly conceived, premature or inappropriate and is potentially harmful to oneself or others (Chamberlain & Sahakian, 2007; Moeller et al., 2001). Impulsive behavior occurs in the general population, but is also a core symptom of a variety of psychiatric disorders including impulse control disorders, personality disorders, ADHD and addiction (Moeller et al., 2001). It is a multidimensional construct that has been suggested to encompass motor, attentional and non-planning aspects of impulsiveness (Moeller et al., 2001; Patton et al., 1995).

Motor impulsivity reflects the tendency to 'act on the spur of the moment' (Moeller et al., 2001; Patton et al., 1995). On a cognitive level motor impulsivity has been linked with response inhibition, i.e. the ability to suppress a prepotent but inappropriate response (Chamberlain & Sahakian, 2007). Response inhibition can be investigated in Go/Nogo paradigms, which require speeded motor responses to one type of stimulus and inhibition of responses to another type of stimulus (Ruchsow et al., 2008). There is consistent evidence that patient groups characterized by high impulsivity are impaired in Go/Nogo task performance, while the relationship between impulsivity and performance in healthy subjects is controversial (Helmers et al., 1995; Keilp et al., 2005).

On a neural level, response inhibition leads to activation of the ventrolateral prefrontal cortex (VLPFC), particularly in the right hemisphere (Aron et al., 2004). However, studies contrasting inhibition and response trials of equal frequency have often reported bilateral VLPFC activation (Liddle et al., 2001; Swick et al., 2008). Only three studies have addressed the relationship between impulsivity and brain activation in a Go/Nogo task in non-clinical subjects (Asahi et al., 2004; Horn et al., 2003; Passamonti et al., 2006). These studies have mostly implicated the right VLPFC, but also the dorsolateral prefrontal cortx (DLPFC). However, they have used blocked designs, which do not allow definition of brain activation specific to response inhibition trials.

Therefore, the aim of the present study was to investigate the relationship between (motor) impulsivity and brain activation during response inhibition employing event-related functional magnetic resonance imaging (fMRI).

2. Methods

Twenty-four healthy volunteers were initially recruited from an academic environment. Subjects were carefully screened for psychiatric disorders by a trained psychiatrist (RG) and psychometric evaluation using the Symptom Checklist 90 Revised (Schmitz et al., 2000). Two subjects were excluded due to clinically relevant psychiatric symptoms. One subject was excluded due to excessive movement during scanning. Thus, twenty-one subjects (11 female, mean age of 27.4±2.3 years) were included in the analysis. Subjects were given the Barratt Impulsiveness Scale 11 (Patton et al., 1995). The BIS is a self-report questionnaire that rates the level of impulsivity. Three subscales describe motor, attentional and non-planning impulsiveness. The study was performed in complete accordance with the Declaration of Helsinki (version 1996) and approved by the University Hospital Heidelberg ethics committee.

In an uncued go/nogo task subjects were required to respond as fast and correctly as possible by pressing a button on a response box to a visual target stimulus (Go) and inhibit the motor response to another stimulus (Nogo). Stimuli were circles and squares. In a trial the stimulus was presented for 120ms followed by a fixation cross for 1340ms. In the 20%Go condition the stimulus requiring response occurred in 20% of trials (*rare-Go* trial). In the 80%-Go condition the stimulus requiring response occurred in 80% of trials, thus building up a prepotent response tendency and requiring inhibition in 20% of trials (*rare-Nogo* trial). This design allowed for a comparison of *rare-Nogo versus rare-Go* trials assuring that the contrast is not confounded by different stimulus frequencies between Nogo and Go trials. For separation of the blood oxygenation level dependent (BOLD) responses the sequence of trials within each block was pseudorandomized with an interval between rare events between 1460ms and 33580ms. In each of the two runs, we used a mixed sequence of 4 20%-Go and 4 80%-Go blocks of 40 trials, separated by 13 s of rest. Overall, 64 *rare-Nogo* and 64 *rare-Go* trials were presented. Each run lasted 9 minutes and 42 seconds.

Images were acquired with a Siemens Trio 3T scanner equipped with a single-channel head coil. We used a rapid echo-planar imaging sequence covering the whole brain with the following parameters: TR 2s, TE 30ms, flip angle 80 degrees, 33 slices (interleaved acquisition), slice thickness 4mm, no interslice gap, in-plane resolution 3.4 x 3.4mm, field of view 220 x 220mm. Each session contained 291 volumes. Analysis was performed with SPM2 (FIL, London) implemented in MATLAB

7 (Mathworks, Sherborn). Standard preprocessing including slice time correction, realignment, normalization and smoothing with a kernel of 10mm FWHM were performed. A general linear model was fitted to the single-subject data. The model included 2 regressors of interest for each condition (*rare-Go, frequent-Nogo, rare-Nogo, frequent-Go*), modelled as events of zero duration convolved with the canonical hemodynamic response function. For group analysis, single subject contrast images were entered into a random-effects model as implemented in SPM2.
For the correlational analysis we performed a two-step procedure assuring independence of ROI definition and correlational analysis (Vul et al., 2009). In the first step, we defined functional ROIs based on t-contrasts for the comparison *rare-Nogo versus rare-Go* trials. ROIs were defined based on the significantly activated voxels within the VLPFC (defined as the inferior frontal gyrus) at a threshold of $p<0.001$ uncorrected. Note that this procedure does not employ a whole-brain regression analysis involving impulsivity scores to identify ROIs and therefore avoids non-indepence errors. In the second step, mean percent signal change for the rare-Nogo trials was extracted from these functional ROIs using marsbar (marsbar.sourceforge.net). The extracted signal change values for each participant were correlated with BIS total and subscale scores (two-tailed Pearson-r, n=21) using Statistica (Statsoft Inc., Tulsa).

<insert figure 1 about here>

3. Results

Overall task performance assessed by d' was lower in the 80%-Go than in the 20%-Go condition (3.97±0.64 versus 5.07±0.14, $t=8.26$, $P<0.0001$). The differences between 80%-Go and 20%-Go conditions in the mean rate of errors were significant for commission errors (14.2±11% versus 0.5±0.7%, $t=5.92$, $P<0.0001$), but not significant for omission errors (0.1±0.2% versus 0.1±0.5%, $t=0.30$, $P=0.76$). There was no significant correlation between BIS total or motor impulsivity scores with task performance as assessed by d' and errors of commission (all $p>0.8$).
Regarding fMRI data the t-contrast rare-Nogo versus rare-Go yielded two clusters of activation in the left VLPFC (MNI coordinates -42 33 -9, cluster size=83, tmax=4.98)

and the right VLPFC (MNI coordinates 39 27 -15, cluster size=15, tmax=4.51) as shown in figure 1.

BIS total score showed a trend-level correlation with left VLPFC signal change during rare-Nogo trials (r=0.4, P=0.07) and no significant correlation with right VLPFC signal change (r=0.18, P=0.44). The BIS motor impulsivity subscale showed a significant correlation with left VLPFC signal change (r=0.58, P=0.006) and right VLPFC signal change (r=0.47, P=0.03). The two other BIS subscales attentional and non-planning impulsiveness were not significantly correlated with VLPFC signal change (all P>0.3)

4. Discussion

Our findings indicate that motor impulsivity is positively correlated with recruitment of the left and right VLPFC during inhibition of a prepotent motor response. On a behavioral level there was no significant correlation between impulsivity and task performance, i.e. subjects with higher impulsivity were not impaired. To our knowledge this is the first study to report a positive correlation between a measure of motor impulsivity and activation of bilateral VLPFC specifically on inhibition trials in a Go/Nogo task.

We used an event-related design allowing the comparison of rare inhibitions with rare responses in a Go/Nogo task, which specifically extracts brain activity related to response inhibition and avoids confounding effects of stimulus frequency. The more prominent left sided activation is in line with findings from studies with equally frequent inhibitions and responses as well as a recent lesion study emphasizing the role of left VLPFC in response inhibition (Swick et al., 2008). Motor impulsivity seemed to be correlated more strongly with left than right VLPFC in our study, but both correlations reached significance.

A positive correlation between VLPFC activation and a measure of impulsivity (Eysenck's Impulsivity Scale) was also found by Horn and colleagues, but was confined to the right hemisphere (Horn et al., 2003). The authors thought this to reflect higher recruitment of this critical area in more impulsive individuals, which would be consistent with our study. However, there was no correlation with impulsivity assessed by BIS. This might be explained in part by the study by Passamonti and colleagues who found different directions of correlation between BIS scores and right VLPFC activation depending on monoamine oxidase-A allele carrier

status (Passamonti et al., 2006). Aside from using blocked designs these studies have focused on BIS total scores, which include the aspects of attentional and non-planning impulsiveness, which are less likely to be specifically related to inhibition of a motor response (Horn et al., 2003; Passamonti et al., 2006).

The only previous study specifically addressing motor impulsivity also employed a blocked design and found a negative correlation between motor impulsivity and signal change in the right DLPFC (Asahi et al., 2004), i.e. more impulsive individuals showed less DLPFC activation during Nogo blocks. The results by Asahi and our own can be reconciled by attributing different functional roles to DLPFC and VLPFC in response inhibition tasks. A reduction of DLPFC activation across Nogo blocks might imply that impulsive individuals have difficulties in applying or maintaining a task set (Sakai, 2008). Since impulsive individuals do not show higher commission error rates, the increased VLPFC activation specifically on response inhibition trials may reflect a compensatory mechanism to maintain task performance.

Our data show that motor impulsivity is the construct most closely linked with VLPFC activation during response inhibition in a healthy population. Furthermore, we suggest that individuals with high motor impulsivity recruit VLPFC more strongly to maintain task performance. Our data support the notion that different types of impulsivity have differential neural bases, which will be important in future studies investigating this construct in patients with psychiatric disorders.

Acknowledgments

Dr. Goya-Maldonado received a final support from the University of Heidelberg (STIBET – DAAD).

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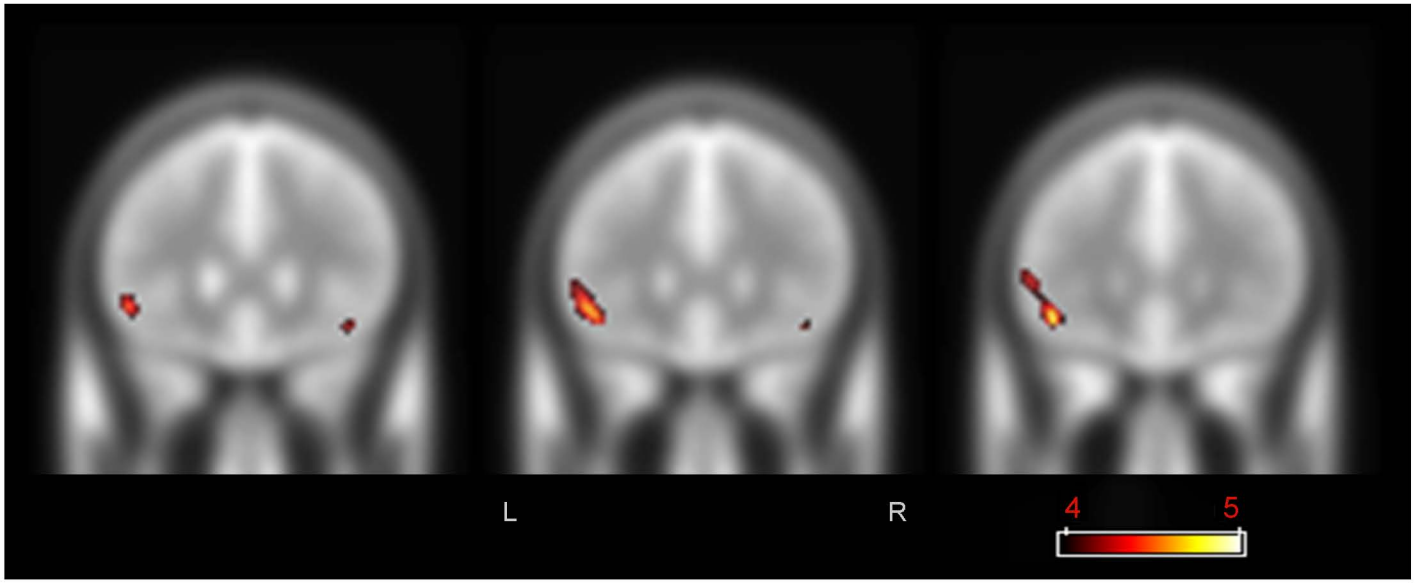
Legend for figure

Figure 1: (Upper panel) Group t-maps for contrast *rare-Nogo vs rare-Go* thresholded at $p<0.001$ (uncorrected) and 10 voxels extension overlaid on averaged structural images of all subjects. (Lower panel) Scatterplots for correlations between Barratt motor impulsiveness scores and mean % signal change on *rare-Nogo* trials in the functional ROIs located in the left and right ventrolateral prefrontal cortex.

Figure 1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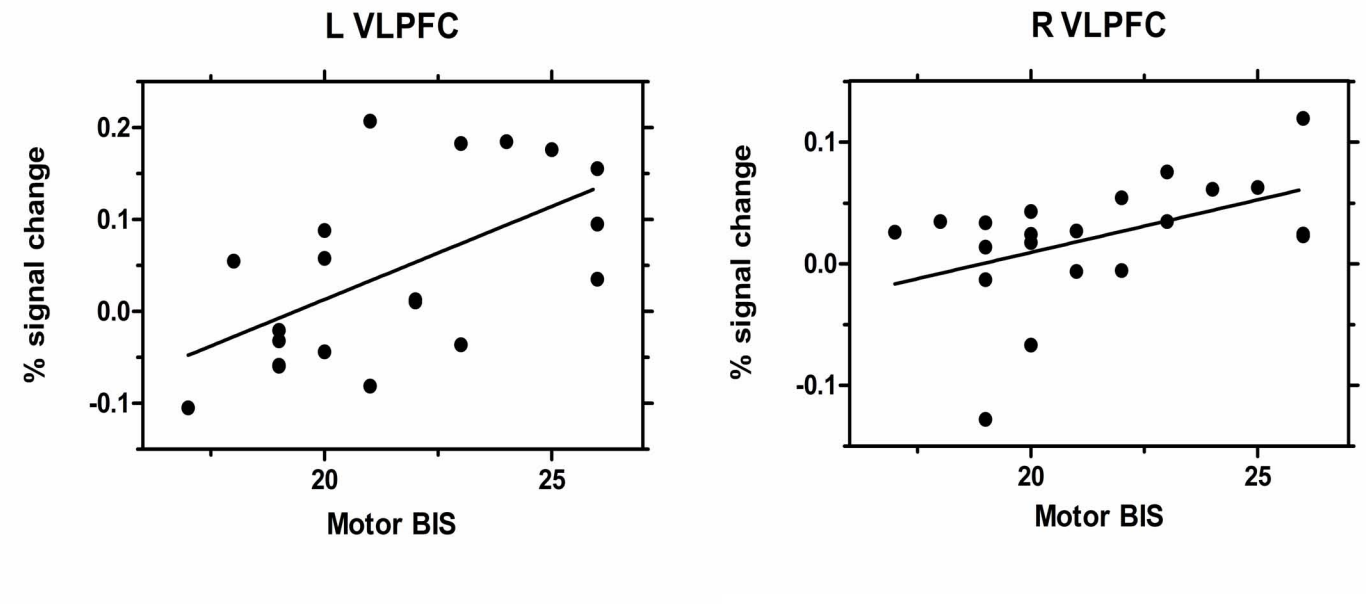
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