Task-Dependent Modulation of Reward and Novelty Processing within Human Ventral Striatum and Midbrain

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Abstract

Computational models of how reward and novelty are coded in the human brain and motivate behavior suggest that there is a close functional relationship between the processing of reward and novelty. One possibility is that stimulus novelty signals an exploration bonus motivating the individual to explore an environment for rewards. However, data as to how reward and novelty functionally interact in the human brain are still missing. The goal of this thesis is to investigate this interaction with an anatomical emphasis on the mesolimbic dopaminergic circuitry, including the substantia nigra / ventral tegmental area complex (SN/VTA) and nucleus accumbens (NAcc). Experiments 1 and 2 investigate the functional interaction between reward and novelty in the mesolimbic system and the influence of related personality traits using functional magnetic resonance imaging (fMRI). The findings are compatible with the notion that novelty serves as an exploration bonus for rewards under conditions where attention is explicitly directed towards reward. This interaction is furthermore depending on personality traits in a way that novelty-seekers were more responsive to novel cues in the absence of reward and needed less reward to boost their memory for novel cues. These observations strongly suggest that novelty seeking is not necessarily based on actual reward-predicting stimulus properties. Experiment 3 investigates how mesolimbic fMRI signals are correlated with actual dopamine (DA) release as measured by positron emission tomography (PET). The results of experiment 3 confirmed that mesolimbic fMRI signals were correlated with DA release within ventral striatum – a notion that has been implied in many studies but has not been demonstrated yet. This latter finding supports the inference that the mesolimbic interactions between novelty and reward signal functional properties of dopaminergic circuitry. The findings of this thesis confirm that novelty and reward processing indeed interact regarding behavioral motivation, and that the mesolimbic responses can be functionally distinguished depending on individual differences in the tendency to seek either for reward or novelty – indicating that both properties are not interchangeable.

Zusammenfassung

Die vorliegende Arbeit befasst sich im Kern mit der neuronalen Verarbeitung von Stimulusneuheit und Belohnung und mit der Frage nach der funktionalen Beziehung beider Prozesse. In verschiedenen Studien wurde eine belohnungsassoziierte Aktivierung in dopaminergen Arealen des Mittelhirns, genauer in der Substantia Nigra (SN) und dem Ventralen Tegmentalen Areal (VTA) sowie im Nucleus Accumbens (NAcc) berichtet. Basierend auf Tierstudien, welche eine vermehrte Aktivität dopaminerger Neurone in Reaktion auf neue Umgebungen und zudem eine gesteigerte Präferenz für diese Umgebungen auch in Abwesenheit von Belohnung berichteten, wurde die Vermutung formuliert, dass Neuheit einen sogenannten 'Explorationsbonus' vermittelt.

In den ersten beiden Experimenten der vorliegenden Arbeit wurde der Einfluss von Neuheit auf die Antizipation von Belohnung mittels funktioneller Magnetresonanztomographie (fMRT) untersucht. In beiden Experimenten wurden die Faktoren Stimulusneuheit (neu vs. bekannt) und Belohnungsantizipation (belohnt vs. neutral) manipuliert. Die Information über die mögliche Belohnung wurde dabei durch den Bildinhalt (Außen- vs. Innenaufnahmen) vermittelt. Jeweils 50 Prozent der belohnten und neutralen Bilder waren am Tag zuvor familiarisiert worden. Das Paradigma ist angelehnt an den 'Monetary Incentive Delay Task', welcher es ermöglicht die Belohnungsantizipation auf einen Hinweisreiz und den tatsächlichen Erhalt der Belohnung getrennt zu untersuchen. Zu Beginn jedes Durchgangs sahen die Probanden ein Bild, welches als Hinweisreiz für die Aussicht auf eine Belohnung in der folgenden Reaktionszeitaufgabe diente. In dieser wurde das Zeitfenster für die Reaktion dynamisch adaptiert, so dass die Erfolgsrate für jeden Probanden bei ca. 75 Prozent lag. Am Ende jedes Durchgangs erhielten die Probanden ein visuelles Feedback, welches in belohnten Durchgängen in Abhängigkeit von der Leistung in der Reaktionszeitaufgabe entweder einen Gewinn oder einen Verlust anzeigte und in unbelohnten Durchgängen stets neutral und damit leistungsunabhängig war. Beide Experimente verwendeten das gleiche Bildmaterial und unterschieden sich lediglich in der Aufgabeninstruktion:

Während die Probanden in Experiment 1 bei der Präsentation jedes Bildes per Tastendruck entscheiden mussten, ob es sich um ein bekanntes oder um ein neues Bild handelt, erfolgte in Experiment 2 eine Entscheidung bezüglich der Belohnungsantizipation. Vierundzwanzig Stunden nach dem fMRT Experiment wurde die Gedächtnisleistung bezüglich aller präsentierten Bilder getestet.

Die Ergebnisse beider Experimente replizierten die mit Belohnungsantizipation assoziierten Aktivierungen in SN/VTA und NAcc. Während der expliziten Belohnungsantizipation (Experiment 2) führte Stimulusneuheit wie erwartet zu einer Verstärkung der mesolimbischen Aktivierung und gleichzeitig zu einer verminderten neuronalen Antwort im NAcc in der darauffolgenden Feedbackphase. Bei impliziter Belohnungsverarbeitung (Experiment 1) war dagegen keine Verstärkung der mesolimbischen Antwort durch Neuheit zu beobachten. In beiden Experimenten wurde die Gedächtnisleistung durch Belohnungsantizipation verbessert. Die Ergebnisse bestätigen somit die ursprüngliche Hypothese, dass Stimulusneuheit nur dann einen Explorationsbonus bereithält, wenn die Aufmerksamkeit explizit auf die belohnungsrelevanten Aspekte des Hinweisreizes gerichtet ist, und dass dieser Effekt über mesolimbische Verbindungen vermittelt wird. Die verlängerten Reaktionszeiten und eine vermehrte Aktivierung des dorsalen anterioren zingulären Kortex und okzipitaler Areale während der expliziten Neuheitsdetektion in Experiment 1 legen die Vermutung nahe, dass hier eine vermehrte Rekrutierung kognitiver Ressourcen erforderlich ist.

Da verschiedene Persönlichkeitseigenschaften mit der Verarbeitung von Belohnung und der Enkodierung von Neuheit in Verbindung gebracht werden, wurden die Ergebnisse der beiden ersten Experimente zusätzlich mittels zweier Persönlichkeitsskalen aus dem Temperament und Charakter Inventar (TCI) analysiert: Belohnungsabhängigkeit (reward dependence) und Neuheitssuche (novelty seeking). Dabei war novelty seeking positiv mit der neuronalen Aktivität in SN/VTA für neue neutrale Bilder und gleichzeitig negativ mit dem belohnungsabhängigen Zugewinn beim Wiedererkennen neuer Bilder assoziiert. Für reward dependence ergab sich dagegen ein positiver Zusammenhang mit der neuronalen Aktivierung für neue belohnte Bilder. Die Ergebnisse der Korrelationsanalyse deuten darauf hin, dass sich der

motivationale Anreiz von Neuheit für 'Novelty-Seeker' sowohl in einer verstärkten neuronalen Antwort in Abwesenheit von Belohnung als auch in einem geringeren Zugewinn in der Gedächtnisleistung durch tatsächliche Belohnung widerspiegelt. Zudem scheint Neuheit für belohnungssensitive Menschen nicht mit Belohnung gleichgestellt zu sein. Neuheit und Belohnung stellen somit offenbar zwei funktionell voneinander unterscheidbare motivationale Konzepte dar.

Um den Zusammenhang zwischen der mesolimbischen Aktivierung im Rahmen von Belohnungsparadigmen und der tatsächlichen dopaminergen Neurotransmission zu untersuchen, wurde ein Belohnungsexperiment unter vergleichbaren Bedingungen sowohl im fMRT als auch im Positronenemissionstomographen (PET) durchgeführt (Experiment 3). Die Analyse der Daten aus beiden Messmodalitäten ergab einen positiven Zusammenhang zwischen der im Rezeptor-Liganden-PET ermittelten belohnungsabhängigen Dopamin-Ausschüttung im ventralen Striatum und der neuronalen Aktivität in SN/VTA und NAcc der gleichen Probanden im fMRT Experiment. Die Ergebnisse aus Experiment 3 stellen somit einen direkten Zusammenhang zwischen fMRT-Aktivierungen im mesolimbischen System und der tatsächlichen dopaminergen neuronalen Transmission her – ein Zusammenhang der in vielen fMRT-Experimenten impliziert aber bisher nicht formell gezeigt wurde – und unterstützen somit die Annahme, dass die Interaktion von Neuheit und Belohnung über das dopaminerge System vermittelt wird.

Die Ergebnisse dieser Arbeit bestätigen die Interaktion zwischen Neuheit und Belohnung unter Beteiligung dopaminerger Neurotransmission und zeigen ausserdem, dass die mesolimbischen Aktivierungen sich in Abhängigkeit von der individuellen Präferenz für Neuheit oder Belohnung unterscheiden. Diese Beobachtung legt die Vermutung nahe, dass Neuheit und Belohnung hinsichtlich ihrer motivationalen Funktion nicht gleichzusetzen oder austauschbar sind.

Contents

Abbreviations

ACC	anterior cingulate cortex
ADHD	attention-deficit/hyperactivity disorder
BAS/BIS	behavior activation/inhibition system
BOLD	blood oxygen level dependent contrast
BP_{ND}	binding potential (non-displaceable)
DA	dopamine
dACC	dorsal anterior cingulate cortex
EEG	electroencephalography
EPI	echo-planar image
ERP	event-related potential
Exp	experiment
ExpE	exploratory excitability
fMRI	functional magnetic resonance imaging
GABA	gamma-aminobutyric-acid
GLM	general linear model
HarmA	harm avoidance
HRF	heamodynamic response function
lPFC	lateral prefrontal cortex
MEG	magnetoencephalography
mPFC	medial prefrontal cortex
NAcc	nucleus accumbens
NovS	novelty seeking
PD	proton density
PET	positron emission tomography
PFC	prefrontal cortex
PPT	peduncolipontine tegmental nucleus
rANOVA	repeated measures analysis of variances
RewD	reward dependence
ROI	region of interest
SN	substantia nigra
TCI	temperament and character inventory
VTA	ventral tegmental area

1. General Introduction

1.1. Reward processing

1.1.1. Biology of reward processing

The processing of reward plays a major role with regard to behavioral motivation in animals and humans. More than 80 years ago researchers started to investigate the basic principles of reward-driven learning (Pavlov, 1927; Skinner, 1958). The quest began using classical and operant conditioning paradigms on the behavioral level and was boosted by the invention of electrophysiological and functional imaging techniques which provided insights into the anatomical and neuronal background of reward-driven behavior.

Since dopamine (DA) is one prominent neurotransmitter in the mammalian brain that contributes to both physiological and cognitive/psychological functions, DA is especially important for the processes investigated in this thesis, i.e. reward and novelty encoding. The cell bodies of dopaminergic neurons are housed in the substantia nigra (SN) and the adjacent ventral tegmental area (VTA) and project to several striatal and cortical regions (see Fig. 1).

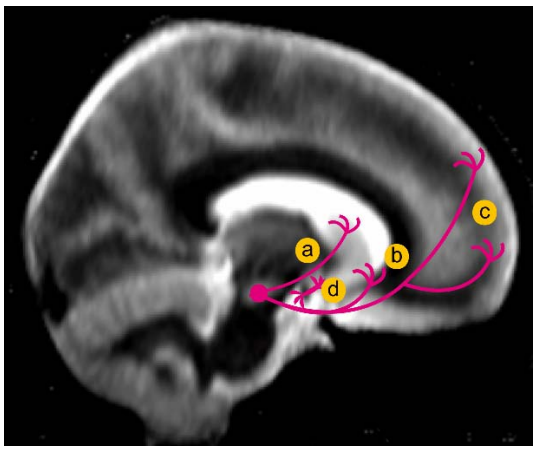


Fig. 1. Major dopaminergic pathways in the human brain. This scheme displays the nigro-striatal projections from midbrain to dorsal striatum with caudate nucleus and pallidum **(a)**, the meso-limbic projections from midbrain to NAcc **(b)**, the meso-cortical projections from midbrain to frontal, temporal, and anterior cingulate cortex **(c)**, and the tuberoinfundibular connection between hypothalamus and hypophysis **(d)**.

Due to the difficulties to clearly segregate the closely connected midbrain structures in the human brain (Björklund and Dunnett, 2007), I will refer to SN and VTA as one complex (see Fig. 2a). Furthermore, I will focus on the mesolimbic (connections from SN/VTA to ventral striatum), as well as on

mesocortical (i.e. connections from SN/VTA to frontal cortex, temporal lobe, and anterior cingulate cortex (ACC)) pathways of the dopaminergic system. One major target region of mesolibic dopaminergic projections is the nucleus accumbens (NAcc) within ventral striatum that is part of the basal ganglia (see Fig. 2b). Since Olds and Milner discovered (more or less accidentally) that animals are driven to excessive self-stimulation behavior via electrodes in the NAcc (Olds and Milner, 1954; Kilpatrick et al., 2000) researchers suggested that appetitive and rewarding events are processed in this region and that it is thus crucial for behavioral motivation.

The key mechanism in mesolimbic reward processing is the phasic activity of dopaminergic neurons in the SN/VTA in response to unpredictable rewards, both to primary (e.g. food) and secondary rewards (e.g. money). This phenomenon was observed in single-cell recordings in animals and conceptualised as the 'prediction-error' signal (Schultz, 1997, , 2002). Furthermore, a phasic DA response is also elicited by reward-predicting stimuli in the absence of an actual reward (Schultz, 2002). With increased learning of cue-reward associations, the initial dopaminergic response to the actual reward decreases and is transferred to the conditioned reward-predicting cue. Both mechanisms, the prediction-error signal to unexpected rewards and the response to the established reward-predicting cues, are associated with phasic DA response in the midbrain and lead to an increase in extracellular DA within NAcc in animals (Ikemoto and Panksepp, 1999; Ikemoto, 2007). A similar mechanism has been observed in intracranial self-stimulation paradigms in rats, where the stimulation of VTA neurons led to increased firing rates of DA neurons in the NAcc (Yun et al., 2004; Cheer et al., 2007). The dopaminergic reward signal in the NAcc is mainly mediated by two different receptor-types: While D2 receptors occupy both the pre- and postsynaptic membrane of the NAcc, D1 receptors are only located on the postsynaptic side. This differentiation is important for the investigation of reward processes by different imaging techniques. During acquisition of the NAcc activation via functional magnetic resonance imaging (fMRI), the signal mainly depends on postsynaptic D1-related transmission (Logothetis, 2002), whereas positron emission tomography (PET) measurements are related to the binding potential of a

specific tracer on D2 receptors (Mawlawi et al., 2001; Martinez et al., 2003; Knutson and Gibbs, 2007). With regard to these different receptor types, Goto and Grace recently reported distinct modulations in NAcc DA release by hippocampal and prefrontal stimulation in rats (Goto and Grace, 2005). While D1 receptor agonists facilitated hippocampus-evoked DA release, D2 receptor antagonists facilitated prefrontal-evoked DA release in the NAcc. This finding is especially crucial for the role of DA regarding the modulation of goal-directed behavior which on its part could also be affected by reward prediction.

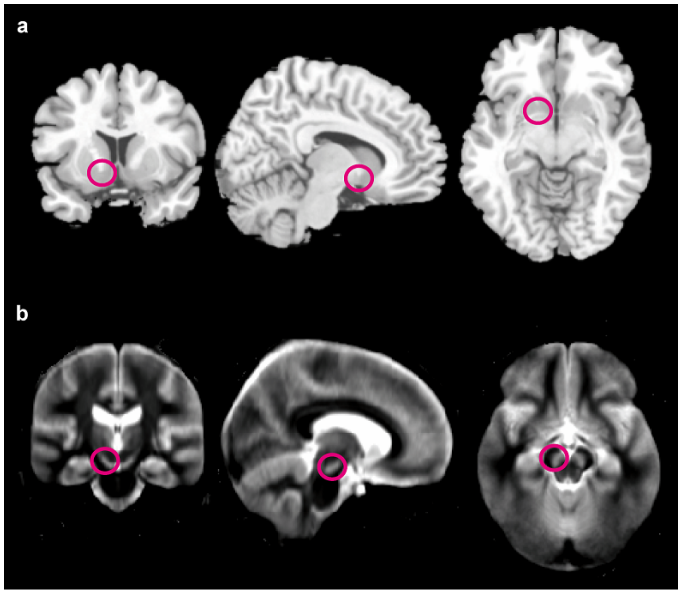


Fig. 2. Anatomical location of two regions associated with reward processing. **(a)** The NAcc as part of the ventral striatum (x y z = -10 10 -8) and **(b)** the SN/VTA within the midbrain (x y z = -10 -18 -14).

Animal studies have shown that at least three further transmitters, i.e. glutamate, gamma-aminobutyric acid (GABA), and norepinephrine vitally contribute to the modulation of the reward-related dopaminergic response in the NAcc (Wu et al., 1993; Vallone et al., 2000; Hjelmstad, 2004; Gerdjikov and Beninger, 2006; Ventura et al., 2007). Although dopaminergic neurotransmission is closely cross-linked to other transmitters I will focus on the DA-system in this thesis.

1.1.2. Research on reward anticipation in humans

Reward paradigms. A large number of human functional neuroimaging studies on reward-related mechanisms have been conducted to investigate brain activity during unexpected rewards and reward anticipation (for review see

Knutson and Cooper, 2005; for review see Delgado, 2007). One of the most prominent reward paradigms is the card-guessing task which has been used in several studies by Delgado and colleagues (Delgado et al., 2000; Delgado et al., 2005). Subjects are presented with a blank card and have to decide if the value on the turned card will be above or below five. After the decision the card is turned around and the actual value appears as a feedback. Dependent on the correctness of their guess, subjects either receive a monetary reward, no reward, or even loose a small amount of money. Another well established paradigm is the monetary incentive delay (MID) task (Knutson et al., 2000; Knutson et al., 2003), which is based on experiments that elicit reward-related VTA neuron activity in monkeys (Schultz et al., 1998). Here, subjects are presented with colored squares or circles serving as cues for a possibly rewarded, punished or a neutral trial. After a variable delay, subjects have to respond to a white target square and receive a positive, negative or neutral feedback depending on whether their reaction time was fast enough. In order to guarantee hit rates of approximately 60% for the rewarded trials, individual mean response times (RT) are assessed before the main experiment and the RT window for the target is adapted accordingly (Knutson et al., 2000). The paradigm can be varied by introducing different reward magnitudes represented by the number of lines within the square or circle cue (Knutson et al., 2005).

Mesolimbic reward response. The typical fMRI response to the reward-predicting cue in these paradigms is an activation of the reward-related regions described above (see Fig. 2), i.e. the SN/VTA and the NAcc (Delgado et al., 2000; Berns et al., 2001; Breiter et al., 2001; Kirsch et al., 2003; McClure et al., 2003; Zink et al., 2004; Wittmann et al., 2005; Preuschoff et al., 2006; Cooper and Knutson, 2008). Furthermore, it has been shown that the NAcc seems to be especially sensitive to differences in the magnitude of reward cues (Knutson et al., 2001a; Knutson et al., 2005). A recent study by Cooper and Knutson found a correlation between NAcc activation and both the valence and salience of the cue (Cooper and Knutson, 2008). The authors reported that NAcc activation was enhanced for the certain prediction of positive outcomes as well as for the uncertain prediction of any outcome, independent of the actual

positive or negative valence. These findings suggest that the NAcc might be furthermore sensitive to prediction-errors as reported for SN/VTA neurons by Schultz (Schultz, 2002). Other authors explicitly reported an accumbal prediction-error signal in response to a deviation from expected outcomes (Pagnoni et al., 2002; Cohen, 2007; Spicer et al., 2007). In normal healthy humans, this prediction-error is based on the paradigmatic unpredictability of the outcome that prevents the subject from learning a constant cue-reward association.

The robust fMRI activation in response to reward-predicting stimuli and unpredicted rewards in the medial midbrain and the ventral striatum are further supported by several PET studies (Thut et al., 1997; Koepp et al., 1998; Pappata et al., 2002; Zald et al., 2004). One of the first studies on reward processing using PET reported a robust change in regional cerebral blood flow within prefrontal cortex (PFC), midbrain, and thalamus when comparing rewarded to neutral experimental blocks (Thut et al., 1997). Since this technique is based on radio-labelled water and thus reflects the changes in blood flow, it does not allow for conclusions regarding actual dopaminergic transmission. However, subsequent studies which used radio-labelled raclopride as DA-specific tracer provided strong evidence for a dopaminergic contribution to reward processing (Koepp et al., 1998; Pappata et al., 2002; Zald et al., 2004). Two studies found an enhanced striatal DA-release in the rewarded compared to the neutral condition holding equal motor requirements (Pappata et al., 2002; Zald et al., 2004) and one study reported DA-release while subjects played a video game (Koepp et al., 1998). Given that raclopride PET measurements depend on the tracer binding to D2 receptors, the results are limited to the striatum and other cortical regions where D2 receptors are located. Thus, it is not possible to visualize the medial midbrain, i.e. the source region of dopaminergic activity.

New approaches relating human reward processing to the dopaminergic system arose from genetic imaging. A recent study reported an influence of two DA-related gene polymorphisms, i.e. the DA transporter (DAT) and catechol-o-methyltransferase (COMT), with regard to individual reward-sensitivity (Yacubian et al., 2007). Furthermore, Kirsch and colleagues reported that the

striatal reward anticipation response is enhanced under the intake of the D2 receptor agonist bromocriptine, but exclusively in carriers of a certain polymorphism (D2 TaqIA), which is associated with lower D2 receptor density (Kirsch et al., 2006).

For the most part, the above described processes refer to the reward anticipation response towards the reward-predicting cue once the cue-reward association has been well established. In these cases, the response to the actual reward (reward outcome) is no longer mediated by the dopaminergic SN/VTA signal but rather evaluated in the dorsal striatum (i.e. caudate nucleus and putamen), as well as in prefrontal and orbitofrontal areas (Knutson et al., 2000; Knutson et al., 2001b; Knutson et al., 2003; O'Doherty et al., 2003a; Spicer et al., 2007).

With regard to the comparability of animal research and human imaging studies it is important to state, that although most studies in humans used secondary reinforcers like money, there is also strong evidence for reward anticipation responses to primary rewards like juice (Berns et al., 2001; Pagnoni et al., 2002; McClure et al., 2007).

Contribution of other regions. The response to rewarding events and reward-predicting stimuli in the dopaminergic midbrain and ventral striatum is modulated by other areas, i.e. PFC, orbitofrontal cortex (OFC), ACC, and amygdala, that are engaged in goal-directed behavior (Glimcher and Rustichini, 2004; Delgado, 2007). These regions receive dopaminergic input from midbrain neurons (Gasbarri et al., 1997) and are also partly connected to the ventral striatum (Groenewegen et al., 1999).

The striatum receives direct projections from the PFC, which is engaged in monitoring the incentive value of reward outcomes (Cardinal et al., 2002; Knutson et al., 2003; Rogers et al., 2004). There is recent evidence, that the reward-related NAcc response is mediated by prefrontal activity via norepinephrine (Ventura et al., 2007). The authors reported earlier that a depletion of prefrontal norepinephrine in mice led to a diminished dopaminergic NAcc response to reward (Ventura et al., 2003). In humans, it has been shown that the activity of the medial PFC is modulated by the probability of anticipated rewards (Knutson et al., 2005). Regarding the actual reward outcome phase,

the PFC contributes to the evaluation of the received reward (Knutson et al., 2003). The medial OFC also projects to the ventral part of the striatum, and thus influences the reward anticipation signal in the NAcc by assessing the predictive value of the stimulus (Berns et al., 2001; Elliott et al., 2004; O'Doherty, 2004; Kringelbach, 2005; Roesch and Olson, 2007). The general function of the amygdala is the processing of emotional or salient stimuli and it is thus engaged in motivational behavior, learning, and memory formation (Fried et al., 2001; for a review see Cardinal et al., 2002; Hariri et al., 2003). With regard to reward processing it has been shown that the amygdala is especially recruited when reward cues are emotional or in another sense salient (Baxter and Murray, 2002; Gottfried et al., 2003; Hommer et al., 2003; Elliott et al., 2004) and thus contributes furthermore to the evaluation of expected values in interaction with the OFC (Holland and Gallagher, 2004). The ACC holds a major role in general decision making and risk evaluation (for review see Bush et al., 2000) and is thus involved in complex decisions regarding different anticipated rewards (Rogers et al., 2004; Preuschoff et al., 2006; Landmann et al., 2007; Marsh et al., 2007). With regard to reward-related midbrain activity, that had been mainly localized in SN/VTA neurons, a recent study on reward-processing reported a prediction-error induced increase of dopaminergic activity of the mesencephalic pedunculopontine tegmental nucleus (PPT) in monkeys (Kobayashi and Okada, 2007), suggesting another reward-responsive input area within the dopaminergic midbrain.

Taken together, there is strong evidence for a distinct network involved in reward-based decision making and learning processes including the dopaminergic midbrain, ventral striatum, frontal cortex, ACC, and to some extent the amygdala (McClure et al., 2004; Delgado, 2007; Landmann et al., 2007; O'Doherty et al., 2007).

1.1.3. Derailment of reward processing

The shift of the mesolimbic DA-response from the time of the reward to the time of the presentation of the cue critically depends upon successful learning of a stimulus-reward association (O'Doherty et al., 2003b; Schonberg et al., 2007). Recent studies have shown that this type of learning is impaired under

conditions of DA deficiency, such as aging (Schott et al., 2007; Weiler et al., 2008), Parkinson's disease (Schott et al., 2007), or DA imbalance, such as schizophrenia (Murray et al., 2007) in humans, as well as in NAcc lesions (Parkinson et al., 2002) and lack of D2 receptors in animals (Tran et al., 2002; Kruzich and Grandy, 2004). Consistently, a deficient reward-learning leads to an enhanced prediction-error in response to the actual reward outcome. Alterations in reward-processing have furthermore been associated with anhedonia in animal models (Bardo and Bevins, 2000; Bevins and Besheer, 2005) as well as with negative mood (Glautier et al., 1998), major depression (Naranjo et al., 2001), and bipolar disorder (Abler et al., 2007) in humans, in a way that patients show a reduced sensitivity and responsiveness to rewards.

Another important derailment of reward-processing, which has been associated with the DA transmission is addiction (van Ree et al., 1999; Comings and Blum, 2000; Everitt and Robbins, 2005). Animal models propose that chronic abuse of substances can lead to neuroadaptive changes in the dopaminergic system and thus facilitates long-term pathology in consuming behavior and reward-learning (Olausson et al., 2003; Kenny et al., 2006). Since the NAcc is crucial for reward-processing, it is likely that its functioning is specifically altered in addiction. In the early phase of substance intake the NAcc responds to the intake as well as to drug-related cues. For humans it has been shown that chronic alcohol abuse causes a downregulation of the involved D2 receptors in the NAcc. This change in sensitivity towards the drug leads to a subsequent increase in consumption and to an alteration in DA-dependent reward prediction that drives the system to overestimate the incentive value of the drug and the related cues (Heinz et al., 2004; Heinz et al., 2005). Furthermore, a recently reported PET study revealed that even nicotine abusers show a decreased availability of striatal D2 and D3 receptors (Fehr et al., 2008). Additionally, there is now evidence that alterations of the D2 receptor density as a result of genetic variation (i.e. the D2 TaqIA polymorphism) are related to the so called 'reward deficiency syndrome' which is closely linked to addiction and craving (Blum et al., 2000; Comings and Blum, 2000; Noble, 2000; Bowirrat and Oscar-Berman, 2005).

1.2. Novelty processing

1.2.1. Research on novelty encoding

The occurrence of a novel event raises and captures attention and promotes a complex cascade of neural processes that are related to visual attention, learning, and memory formation (Ranganath and Rainer, 2003). The drive to explore novel objects and environments is an essential mechanism for most species to develop (Knutson and Cooper, 2006). Given the strong diversity in the concept of novelty, there are several different approaches to describe and manipulate it in experimental settings (Ranganath and Rainer, 2003; Nyberg, 2005). The standard classifications for experimentally manipulated novelty are *stimulus novelty*, *contextual novelty,* and *associative novelty. Stimulus novelty* implies that the current stimulus and its properties are completely unknown to the subject. The criteria of such a conceptualisation can be more or less rigorous. One could imagine a pink elephant for example, which could indeed count as novelty, but still holds familiar attributes. A typical paradigm to investigate stimulus novelty is the presentation of items the subject has seen before (termed *familiars*) intermixed with items the subject has never seen before (termed *novels*) (see e.g. Tulving et al., 1996; Kirchhoff et al., 2000). C*ontextual novelty*, on the other hand, can be manipulated by presenting a series of similar items to the subject. Some of these stimuli deviate regarding their stimulus properties, e.g. colour, size, or loudness and are thus termed contextual novels or 'oddballs' (see e.g. Suwazono et al., 2000; see e.g. Bunzeck and Duzel, 2006). A third way to manipulate novelty is *associative novelty*. Here previously presented stimuli are later presented in a different way, e.g. in a new spatial formation (see e.g. Duzel et al., 2003; see e.g. Duzel et al., 2004; Schott et al., 2004).

Stimulus novelty. *Stimulus novelty*, which can be manipulated by the intermixed presentation of familiarized and novel items, is typically associated with an enhanced activation in the medial temporal lobe, which has been described as a 'novelty signal' (Tulving et al., 1996; Rainer and Miller, 2000; Ranganath et al., 2000). The gradual decrease of this signal, that is associated with the number of stimulus repetitions, has thus been termed 'repetition

suppression' (Wiggs and Martin, 1998; Henson and Rugg, 2003), 'response suppression' (Desimone, 1996), or adaptation (Ringo, 1996). Repetition suppression is based on a stimulus-specific reduction in the firing rate of the involved neurons and occurs during various task types, e.g. delayed matching-to-sample (Miller et al., 1996), classification (Sobotka and Ringo, 1994), and passive viewing tasks (Miller et al., 1991). Ringo provided a review of the occurrence and conditions of this phenomenon in several cortical and subcortical regions regarding single-cell measurements in monkeys (Ringo, 1996). He assumes that the repetition-related decrease in neural activity allows for a more efficient encoding of novel items through reduced interference with familiar material. The suggested underlying mechanism of the neural response reduction and the improved processing of repeated stimuli is a so called 'dropping out' effect of neurons regarding familiar object representations (Wiggs and Martin, 1998; Ranganath et al., 2003). The higher neural efficiency might be based on synaptic plasticity (Grunwald et al., 1999; Stark and McClelland, 2000). Regarding the function of successful novelty encoding, repetition suppression provides support for the 'novelty-encoding hypothesis' (Tulving et al., 1994; Tulving et al., 1996; Habib et al., 2003; Kormi-Nouri et al., 2005). Tulving suggests that novelty encoding reflects an early stage in the formation of long-term memories and that the probability of storage depends on the novelty of the signal. It has further been reported, that the decrease in response to stimulus repetitions in neurons of the perirhinal cortex in monkeys is especially crucial for judgements about the novelty/familiarity of the stimulus (Brown and Xiang, 1998).

Observations of Ihalainen and colleagues provided important insights into the relationship between the novelty signal and dopaminergic neurotransmission (Ihalainen et al., 1999). The researchers reported hippocampal and prefrontal DA release in mice, while the animals were exposed to a novel cage environment. There is further evidence from earlier single-cell recordings in monkeys that midbrain DA neurons respond when novel a compartment is opened (Ljungberg et al., 1992).

Given that the blood oxygen level-dependent (BOLD) signal reflects the underlying neural mechanisms relatively well (Logothetis, 2002), it enables us

to compare the data of human fMRI studies to electrophysiological animal research (Henson and Rugg, 2003; Ranganath and Rainer, 2003). Hence, the enhanced neural activity for novel stimuli on the one hand and the reduction in neural firing rates in response to stimulus repetition on the other hand, are related to the increase and decrease in the BOLD signal in novelty-responsive regions, respectively (Ranganath and D'Esposito, 2001).

Both, novelty signal and repetition suppression have been described in several imaging studies in humans (for a review see Knight and Nakada, 1998; for a review see Ranganath and Rainer, 2003; Nyberg, 2005). The most responsive regions for novelty/familiarity encoding are the hippocampal formation (including entorhinal cortex, dentate gyrus, CA1, CA2, CA3, and subiculum) and the PFC (Stern et al., 1996; Saykin et al., 1999; Menon et al., 2000; Ranganath and D'Esposito, 2001; Rombouts et al., 2001; Downar et al., 2002; Yamaguchi et al., 2004; Meltzer and Constable, 2005; Bunzeck and Duzel, 2006; Wittmann et al., 2007). Several studies reported additional novelty-associated activation changes within the parahippocampal region (Stern et al., 1996; Kirchhoff et al., 2000; Menon et al., 2000; Rombouts et al., 2001), the anterior insula (Rombouts et al., 2001; Downar et al., 2002), the ACC (Saykin et al., 1999; Kirchhoff et al., 2000; Rombouts et al., 2001; Downar et al., 2002), the fusiform gyrus (Stern et al., 1996; Kirchhoff et al., 2000; Rombouts et al., 2001) and the medial midbrain (Bunzeck and Duzel, 2006; Wittmann et al., 2007). Most of these studies used familiar and novel picture stimuli, but the effect could also be demonstrated for other stimulus types, i.e. words (Saykin et al., 1999; Kirchhoff et al., 2000; Meltzer and Constable, 2005), auditory and tactile stimuli (Downar et al., 2002).

Similar repetition suppression effects have been found using PET cerebral blood flow measurement within medial temporal lobe and prefrontal regions (Tulving et al., 1996; Badgaiyan et al., 1999) and in electroencephalography (EEG) experiments, where stimulus repetitions led to a decrease of the initially evoked posterior gamma activity and phase synchrony (Gruber et al., 2004).

There are furthermore pharmacological studies linking the repetition suppression to cholinergic neurotransmission. Thiel and colleagues reported a reduction of the difference in BOLD signal between novel and familiar items

under the influence of cholinergic antagonists (Thiel et al., 2001; Thiel et al., 2002).

Contextual novelty. Another important aspect in novelty processing is the encoding of *contextual novelty*. In contrast to stimulus novelty, which is defined by the absolute novelty of a stimulus, contextual novelty is about the temporal occurrence within a stimulus stream. The most common paradigm to investigate contextual novelty is the 'oddball paradigm', in which the majority of stimuli is familiarized and a few novel items are presented at unpredictable time points. Thus, the two major characteristics of the construct are the rareness and the unpredictability of the novel oddballs, which in general lead to an initial 'orienting response' (Sokolov, 1963; Corbetta and Shulman, 2002; Sokolov et al., 2002). The occurrence of oddball stimuli has been frequently associated with a particular event-related potential (ERP) component, the P300, which has been initially reported in human subjects by Sutton and has later been alternatively termed 'novelty P3' (Sutton et al., 1965; Courchesne et al., 1975; Squires et al., 1975; Suwazono et al., 2000; Friedman et al., 2001). The short latency of the P300 component after stimulus onset indicates a rapid modulation of processes involved in novelty encoding (Ranganath and Rainer, 2003).

One important implication on the behavioral level arising from the nature of contextual novelty is the enhanced memory for contextual deviant stimuli, which has been initially reported by von Restrorff and was thus later termed the 'von Restorff' effect (von Restorff, 1933; Johnston et al., 1990; Johnston et al., 1993; Hunt, 1995; Parker et al., 1998; Kishiyama et al., 2004). In the original paradigm, subjects are presented with a series of similar items, which is interrupted by few items deviating concerning one or more stimulus properties. In a subsequent memory test, contextual novel items are associated with a higher recognition probability (Nyberg, 2005). When investigating this effect by means of functional imaging techniques, the hippocampus turned out to be the crucial region for the enhanced memory performance promoted by contextual novelty (Nyberg, 2005). Parker and colleagues observed that the 'von Restorff' effect could be abolished by a disruption of the projections between perirhinal and frontal regions in monkeys (Parker et al., 1998). A recent study using the

'von Restorff' paradigm in amnestic patients provided evidence that the advantageous memory effect for contextual deviant items is diminished or even lost under conditions of hippocampal impairment (Kishiyama et al., 2004).

The orienting response to unpredictable stimuli has been furthermore linked to the concept of 'deviation of expectation' (Downar et al., 2000; Huettel et al., 2002; Strange et al., 2005; Petrides, 2007). Strange and colleagues reported distinct regions that are responsive either to the entropy or to the surprise information in a stimulus stream (Strange et al., 2005). Here, entropy is determined as the expected predictability in the stimulus stream, reflecting the average surprise over all events, whereas surprise is related to the predictability of a single event. While the anterior hippocampus was found to be sensitive to the entropy information, surprise-related responses were found in several cortical and subcortical regions closely linked to the classical visual attention network (Knight and Nakada, 1998; Corbetta and Shulman, 2002) – including the fusiform gyrus, parietal and frontal cortex, and the thalamus (Strange et al., 2005). Other authors found similar activation patterns within frontal cortex for contextual deviant stimuli within a stimulus stream (Kirino et al., 2000; Huettel et al., 2002). With regard to the results on repetition suppression described above, there is evidence for comparable habituation processes in response to contextual deviant stimuli (Strange and Dolan, 2001; Yamaguchi et al., 2004).

Two recent studies in humans provide evidence for a contribution of dopaminergic neurons in the SN/VTA in the midbrain employing paradigms with both stimulus and contextual novelty (Bunzeck and Duzel, 2006; Wittmann et al., 2007). Bunzeck and Duzel (2006) found that absolute coding of stimulus novelty, i.e. novel stimuli compared to other oddballs, led to an activation in SN/VTA, whereas contextual novelty alone, i.e. neutral oddballs compared to standard stimuli, did not activate this region. In the hippocampus, novel oddballs elicited higher activation compared to neutral oddballs (Bunzeck and Duzel, 2006). Another study that relates novelty encoding to dopaminergic midbrain neurons used a novelty/familiarity encoding paradigm, in which cues predicted the appearance of novel or familiar pictures, respectively (Wittmann et al., 2007). Here, SN/VTA was activated by cues predicting novelty as well as

by unexpected novel cues, which had been preceded by familiarity-predicting cues. The hippocampus was also responsive to novelty-predicting cues and showed increased activation for novel pictures per se, regardless of the predicting cue.

Associative novelty. *Associative novelty*, as a third classification, has been investigated in several studies using object-place association paradigms in animals (Wan et al., 1999; Jenkins et al., 2004). Presenting rats with familiar stimuli in a new arrangement, Jenkins and colleagues (2004) found an increase of the immediate early gene c-fos within the hippocampus, especially in CA1, CA3, and dentate gyrus. This marker has been previously established as a correlate of neuronal activity in animal research (Jenkins et al., 2004). Imaging studies in humans provide evidence for the contribution of the hippocampal formation during encoding of associative novelty (Duzel et al., 2003; Schott et al., 2004; Kohler et al., 2005). Furthermore, Schott and colleagues reported an additional increase of activation within medial midbrain (SN/VTA) by associative novelty (Schott et al., 2004), comparable to the activations in response to stimulus novelty described above (Bunzeck and Duzel, 2006).

1.2.2. Biology of novelty encoding

Since it has been shown that the novelty-dependent DA release in the VTA can be abolished by interrupting the connection between hippocampus and VTA (Legault and Wise, 2001) it is likely that the VTA response to novel stimuli can be traced back to the hippocampus. The novelty signal is suggested to emerge through the comparison of stored information and new sensory inputs. It has been suggested that the region in which this comparison is carried out might be the CA1 layer in the hippocampus (Vinogradova, 2001). The model of Lisman and Grace (2005) proposes that information about previous events that is stored in the CA3 layer provides predictions about future events and projects to the CA1 layer (Lisman and Fallon, 1999; Lisman and Grace, 2005). These predictions might then be compared to the incoming signals from the cortex reflecting the sensory reality which should lead to a novelty detection signal in case of actual novel events. The next step in novelty processing is the transmission of the signal to the VTA via the hippocampal subiculum. This

hypothesis has been supported by the observation that the stimulation of the subiculum itself led to an enhanced activation of VTA neurons (Floresco et al., 2001; Floresco et al., 2003). There are at least two further relay regions on this pathway, the NAcc and the ventral part of the pallidum. It has been shown that the DA signal can be interrupted by the application of glutamate antagonists into the NAcc (Floresco et al., 2001; Gerdjikov and Beninger, 2006). Other studies provide evidence for an inhibiting influence on the VTA through GABAergic neurons of the ventral pallidum (Mogenson, 1993). On the basis of these studies, Lisman and Grace suggest that the novelty signal is projected from the subiculum to the NAcc via glutamatergic synapses, which then inhibits the ventral pallidum via GABA and withdraws its tonic inhibition from the DA-neurons within VTA (Lisman and Grace, 2005). From this perspective, the hippocampal novelty signal provides a feed-forward signal for dopaminergic transmission in the midbrain.

1.2.3. Alterations of the novelty signal

Given that novelty detection depends on dopaminergic neurotransmission, it appears plausible that alterations in the DA system and the involved regions influence the encoding process. There is recent evidence that the integration of the hippocampal-VTA loop during encoding of stimulus novelty is affected by age-related degenerations of both structures (Bunzeck et al., 2007). Based on findings on impairment of hippocampal memory formation in psychiatric disorders (for review see Shenton et al., 2001), there are approaches to link differences in novelty processing and repetition suppression to schizophrenia (Jessen et al., 2002). In keeping with this notion, Jessen and colleagues (2003) found reduced hippocampal activation during encoding of novel words as well as during recognition in schizophrenic patients (Jessen et al., 2003).

1.2.4. Novelty exploration bonus

It is assumed that SN/VTA neurons respond to biologically salient events in sense of rewards, e.g. natural or learned reinforcers, but are also sensitive for other salient events (Horvitz, 2000; Nicola et al., 2004; Robbins and Everitt, 2007) and especially towards stimulus novelty (Schott et al., 2004; Bunzeck

and Duzel, 2006) and even towards the anticipation of novelty (Wittmann et al., 2007).

These findings are in line with previously reported animal models suggesting that novelty enhances learning in so called 'place conditioning paradigms', in which rats showed an increased preference for environments that had been previously paired with novel objects (Pierce et al., 1990; Bardo et al., 1996; Bevins et al., 2002; Bevins and Besheer, 2005). It has been suggested that novelty in the absence of actual primary rewards might be intrinsically rewarding (Bevins and Besheer, 2005). Another hypothesis based on animal research is that novelty might compete with other rewarding stimuli and abolish their rewarding effect (Higgins, 1997). This phenomenon has been impressively demonstrated in self-administration paradigms with amphetamine and other drugs in rats, where the presentation of novel stimuli reduced the number of self-administered infusions of the rewarding substance (Klebaur et al., 2001b; Cain et al., 2004; Cain et al., 2006a). These models are supported by the observation that stimulus novelty is associated with enhanced attentional modulation (Ljungberg et al., 1992), increases in dopaminergic activity (Ihalainen et al., 1999), and hippocampal memory formation in animals (Li et al., 2003).

With regard to these phenomena, Kakade and Dayan (2002) proposed a model in which novelty might act as an 'exploration bonus' and provides a signal for motivating organisms to maintain exploration in novel environments for new sources of reward (Dayan and Sejnowski, 1996; Kakade and Dayan, 2002). Importantly, the authors assumed that this effect of novelty is 'hard-wired' rather than a result of learning. Based on the finding of Braver and colleagues, Kakade and Dayan suggested that novelty-based DA-release might gate stimulus information into working memory to allow for the storage of a new stimulus until its potential rewarding properties are evaluated (Braver et al., 1999; Kakade and Dayan, 2002). It should be noted that Kakade and Dayan distinguish an 'exploration bonus' from a 'novelty bonus', which describes the possibility that novelty has rewarding properties itself rather than promoting further exploration of new environments (Kakade and Dayan, 2002).

There is another line of argumentation that emphasizes the influence of dopaminergic modulation on the motivation to receive a reward, which is associated with the incentive salience of a predicting cue (appetitive) rather than the hedonic impact of the actual reward (consummatory, Berridge, 2007). These incentive-related aspects of motivation are held to modify approach behavior and have recently received attention in theories regarding the functional role of the mesencephalic DA system. Robbins and Everitt extended Berridge's view proposing a more general framework of DA functions in terms of an 'energetic' construct that modulates the strength and frequency of actions (Robbins and Everitt, 2007). Following the authors assumption, DA might be a resource that is provided dependent on the required effort to receive a reward and stimulus novelty might energize exploratory behavior by increasing response strength in the search for rewards (Salamone et al., 2005; Niv et al., 2007; Robbins and Everitt, 2007).

1.3. On memory formation

1.3.1. Memory systems

In general, human memory function is determined as the ability to encode, store, and retrieve information. Resulting from the obvious variability in type and content of memories, there are several classification systems depending on the actual content, encoding situation, and time span of storage (Squire et al., 2004). The first important classification depends on the temporal components of memory formation. The shortest type of 'storing' is the *sensory memory*, which refers to the first 500 ms of stimulus encoding. The time span ranging from more than 500 ms to one minute is defined as *short-term memory* and provides the working memory storage for ongoing tasks, e.g. to keep a phone number in mind. All longer lasting memories are assigned to the *long-term memory*, which is believed to be able to last forever.

One prominent way to describe the different contents of long-term memories is the separation in *explicit* (*declarative*) *memory* including semantic and episodic contents, and *implicit* (*non-declarative*) *memory* including procedural and conditioning-based contents (Squire et al., 2004). *Semantic*

memory contains knowledge about facts independent of the time or space in which they had been acquired, whereas *episodic memory* refers to previously experienced events and the associated personal feelings together with time and space of acquisition. The *implicit memory* includes automated skills and procedures (*procedural memory*) as well as conditioned stimulus-reaction associations and habituation.

The two memory types that are going to be discussed in this thesis are the *episodic memory*, which is crucial for the recollection of previously encoded natural scenes, and the *conditioning-based memory*, which is especially important with regard to implicit learning of cue-reward associations.

1.3.2. DA and memory formation

The major role of the hippocampus in long-term memory formation is supported by animal studies in which recognition memory of monkeys is impaired after damage to the hippocampal region (Zola-Morgan et al., 1989). Transferring this to humans, there is evidence that patients suffering from hippocampal lesions have pronounced deficits in episodic long-term memory while the semantic memory is not or marginally impaired (Vargha-Khadem et al., 1997). With regard to later recognition of previously encoded information, the medial temporal lobe is crucial for the dissociation between novel and familiar contents (Eichenbaum, 2000; Squire et al., 2004; Eichenbaum et al., 2007).

The general striatal and cortical function of the DA signal can be described as a gating and focussing signal that enhances and modifies coincident inputs on postsynaptic neurons. There is recent evidence that this gating function is linked to neuronal plasticity and thus contributes to learning and memory enhancement (Schultz, 2002). Gurden and colleagues found that the stimulation of VTA neurons led to an enhancement of long-term potentiation (LTP) in the connections between hippocampus and PFC in rats. Furthermore, infusion of a D1 receptor agonist into PFC led to similar effects on LTP (Gurden et al., 1999; Gurden et al., 2000). These findings provide evidence for a dopaminergic contribution to LTP in the hippocampal-PFC pathway. Here, the underlying mechanism of LTP is a postsynaptic signal cascade driven via NMDA (N-methyl D-aspartate) receptor activity in the CA1 layer of the

hippocampus (Frey et al., 1991; Sajikumar and Frey, 2004). Additional to plastic neuronal changes, firing rates and the population of DA-neurons can be modulated by activation via NMDA receptors within hippocampus and brainstem (Floresco et al., 2001; Lodge and Grace, 2005). In these studies it has been demonstrated that NMDA infusion into the hippocampal ventral subiculum led to a recruitment of more DA-neurons while an analogous infusion into the PPT in the brainstem led to increases in the firing rate of DA neurons in rats. Linking these findings to human memory functions, a study with healthy subjects revealed that the administration of L-DOPA improved memory performance for pseudowords (Knecht et al., 2004). There is further evidence from genetic imaging that carriers of a genotype that is associated with lower COMT activity (Met/Met allele at codon 108/158) show higher episodic memory performance compared to carriers of the Val allele (de Frias et al., 2004). Schott and colleagues recently demonstrated that a polymorphism in the DA transporter gene (DAT) was related to alterations in the SN/VTA activation during successful episodic memory encoding (Schott et al., 2006). Notably, apart from the specific memory-related DA function, there is recent evidence that DA is associated with enhanced neuronal plasticity formation during transcranial stimulation of the motor cortex (Kuo et al., 2007).

1.3.3. Contributions of reward and novelty to memory

Reward and memory. Since both reward-processing and memory formation are strongly linked to dopaminergic neurotransmission, it is very likely that memory formation can be modulated during reward-based instrumental learning paradigms (Packard and Knowlton, 2002; O'Doherty, 2004; O'Doherty et al., 2007). The upward path of the hippocampal-VTA loop as proposed by Lisman and Grace can be modified by rewarding properties or general salience of the stimulus via limbic inputs to the PPT which is closely connected to the VTA via glutamatergic synapses (Lisman and Grace, 2005). The PPT receives projections from PFC and amygdala and thus provides a gate for multifaceted information about the affective value or general salience of a stimulus. Recent imaging studies provide evidence, that episodic encoding of reward-predicting stimuli and the accompanying formation of implicit memory is enhanced

through reward-related signals in SN/VTA and NAcc reflecting dopaminergic neurotransmission (Wittmann et al., 2005; Adcock et al., 2006; Schott et al., 2006). Furthermore, other studies propose a dopaminergic influence on other memory types, e.g. working memory (O'Reilly and Frank, 2006). It has been shown that activation in working memory-related regions, i.e. dorsolateral PFC and lateral frontopolar areas, was enhanced in a high load condition (Pochon et al., 2002). The same task associated with reward led to a similar pattern and additional activations within medial frontal pole and medial temporal lobe.

Novelty and memory. Given that LTP-based memory enhancement is driven by DA (Frey et al., 1991; Sajikumar and Frey, 2004), and that the hippocampus receives dopaminergic input from SN/VTA (Scatton et al., 1980), the novelty signal is likely to promote memory processing. Since the VTA neurons are released from the inhibiting influence of the pallidum, dopaminergic projections ascend to the hippocampal CA1 layer and the subiculum – forming the upward pathway of the hippocampal-VTA loop proposed by Lisman and Grace (2005). Li and colleagues have actually demonstrated that the exposure to a novel environment facilitates DA-dependent LTP induction in CA1 via D1-like receptors in rats (Li et al., 2003). This facilitation thus promotes synaptic plasticity and an efficient storage of the new spatial information into long-term memory. In line with these observations, Moncada and colleagues have recently reported that exposure to a novel environment enhances long-term consolidation in an inhibitory avoidance training (Moncada and Viola, 2007). Here, a behavioral tagging process was enhanced in which plasticity-related proteins are suggested to stabilize the memory trace in rats. Recent evidence from human imaging studies brought analogous results. It has been reported that incremental learning can be enhanced in the context of novelty (Fenker et al., 2008) and that the cued anticipation of novelty promotes later recollection of the novel stimulus by enhancing hippocampus-driven memory formation (Wittmann et al., 2007).

1.4. Inter-individual differences

In this thesis, I will focus on two personality scales, i.e. *novelty seeking* (*NovS*) and *reward dependence* (*RewD*), with regard to novelty and reward processing. These scales are partly based upon two major personality theories which should be introduced very briefly. Gray proposed two main motivational systems to be crucial for human behavior and regulation of responses to environmental changes (Gray, 1970, , 1991): the behavior activation system (BAS) and the behavior inhibition system (BIS). The BIS is associated with anxiety and withdrawal behavior in response to threatening situations and is thus sensitive to punishment and responsible for negative feelings. Contrary, the BAS should in general regulate goal-directed approach behavior and is thus sensitive to signals of reward and responsible for positive feelings (Carver and White, 1994). Linking these constructs to neurotransmitter systems in the brain, it has been shown that alterations within the BIS system are related to changes in norepinephrine levels (Santagostino et al., 1996), whereas the BAS system is closely linked to dopaminergic neurotransmission (Stellar and Stellar, 1985).

A second important approach to describe inter-individual differences is based on Cloninger's personality scales (Cloninger, 1986, , 1987, , 1988). In his Temperament and Character Inventory (TCI) Cloninger proposed three main temperament factors, i.e. *NovS*, *RewD*, and harm avoidance (*HarmA*). One subscale of *RewD* (named *persistence*) was later separated and established as an additional independent dimension (Cloninger, 1994). Similar to Gray's BIS/BAS system, Cloninger assumed these traits to be responsible for distinct behavioral functions like activation, inhibition, and maintenance (Cloninger, 1994). *NovS* is supposed to regulate approach behavior to novel and salient events. While *RewD* might regulate the adherence to the established stimuli-reward associations, *HarA* might reflect the tendency to respond to aversive stimuli and their predictive signals (Cloninger, 1987). Monoamine neurotransmitter systems, i.e. DA, serotonin, and norepinephrine, are considered to be fundamental for the characteristics of these personality traits (Cloninger, 1986, , 1987, , 1988). *NovS* is suggested to be related to dopamingergic neurotransmission in a way that a low basal firing rate of DA

neurons is associated with a higher postsynaptic DA receptor sensitivity and high *NovS* scores, whereas high firing rates are associated with a postsynaptic downregulation and lower *NovS* scores. *HarA* might rather be linked to the serotonergic system, with high presynaptic serotonin release and a postsynaptic downregulation of receptor sensitivity predicting high *HarA* scores. Furthermore, high scores in *RewD* are proposed to be related to low basal firing rates of noradrenergic neurons that are associated with a higher postsynaptic norepinephrine sensitivity. Although several studies in animals (Pierce et al., 1990; Bardo et al., 1996) and humans (Netter et al., 1996; Benjamin et al., 2000; Hansenne et al., 2002) support the core assumptions of the original model, the specific relationship between neurotransmission and these personality traits remains unclear (Paris, 2005).

1.4.1. Novelty seeking

Based on the assumptions that the response to novelty is a trait and that novelty processing is dependent on DA, differences in *NovS* behavior should be reflected in alterations of the DA system. There is some evidence from animal models, that responses to novelty depend on the environment in which the animals had been reared. Rats that had developed in enriched environments, i.e. with high sensory stimulation, were later less responsive to novel stimuli and showed faster habituation (Zimmermann et al., 2001; Cain et al., 2004; Cain et al., 2006b; Cain et al., 2006a). A recent study by Stead and colleagues provides evidence for a strong heritability of *NovS* behavior in rats and the phenotypic differences in emotional reactivity between high and low novelty responders (Stead et al., 2006).

The limitation, when relating those animal models to human behavior, is the indirect measurement of *NovS* behavior by means of performance in behavioral tests, e.g. activity in novel environments, observation time regarding novel objects, novelty preference tests, head-dipping on a hole-board (Kliethermes and Crabbe, 2006). We will never get the animal to fill in a personality questionnaire. Another problem in assessing *NovS* behavior in animals as well as in humans is the strong relation to motor activity and stress during exposure

to novel stimuli and environments which has to be controlled (Piazza et al., 1991a; Kliethermes and Crabbe, 2006).

One prominent approach to link human personality traits to neurotransmission is the pharmacological challenge test, in which specific transmitter agonists are utilized to release a marker substance (e.g. growth hormone) and thus allows the assessment of the transmitter system responsivity (Netter et al., 1996; Hansenne et al., 2002; Stuettgen et al., 2005). Hansenne and colleagues found that *NovS* could actually be linked to the DA system in a way that the release of the growth hormone in response to apomorphine, a D2 receptor agonist, is associated with high *NovS* scores (Hansenne et al., 2002). One study reported that high *NovS* scores are associated with lower prolactin levels as assessed in a challenge test with mazindol, i.e. a DA and norepinephrine reuptake inhibitor (Stuettgen et al., 2005). On the basis of the inverse relationship between DA and prolactin distribution the authors suggested that *NovS* is related to higher dopaminergic activity. A PET study of Leyton and colleagues supports this relationship by reporting a high positive correlation between a representative *NovS* subscale (i.e. *exploratory excitability*) and amphetamine-induced increases in striatal DA-levels in healthy subjects (Leyton et al., 2002). These findings can be well related to Cloninger's initial personality trait theory, stating that novelty-seekers in fact show a low baseline activity of DA resulting in a high postsynaptic DA sensitivity, which is mainly associated to D2 receptor activity (Cloninger, 1988). Another approach to link *NovS* to biological markers is the investigation of genetic variations. It has been recently shown, that the Met/Met 108/158 allele in the COMT polymorphism is associated with higher *NovS* scores in healthy subjects (Golimbet et al., 2006) and that variation in the DRD4 receptor gene are associated with *NovS* scores, i.e. the 2- and 5-repeat allele variations were associated with higher *NovS* scores compared to all other repetition types (Ekelund et al., 1999).

There is strong evidence from animal and human research for a relationship between *NovS* and the risk of substance abuse (Wills et al., 1994; Bardo et al., 1996; Howard et al., 1997; Cain et al., 2005) and that therefore a biological

disposition of *NovS* might serve as a predictor for 'drug seeking behavior' (Helmus et al., 2001; Leyton et al., 2002).

These findings together with the evidence for dopaminergic contribution to novelty encoding stated above support the hypothesis, that alterations can be traced back to either genetic variations or early environmental conditions that might lead to differences in DA transmission.

1.4.2. Reward dependence

Animal studies investigating inter-individual variations of sensitivity to rewards (for review see Bardo and Bevins, 2000) are based on conditioning paradigms using different primary rewards for conditioned place preference or self-stimulation paradigms using electrical stimulation and different types of stimulants (e.g. amphetamine, nicotine, caffeine), opiates (e.g. heroin, morphine, methadone), and other drugs (e.g. diazepam, haloperidol, LSD). Reduced reward sensitivity in animals has been associated with exposure to chronic stress (Willner et al., 1987) and psychopathological syndromes that are linked to depressive disorder, i.e. learned helplessness (Vollmayr et al., 2004; Shumake et al., 2005).

Similar to animal models, variations in *RewD* in humans have been linked to differences in the processing of rewards and again to substance abuse. A recent study in Korean female subjects (Lee et al., 2007) found a relationship between the D2 TaqIA polymorphism and reward responsiveness assessed via Gray's BAS-RR scale (Gray, 1970, , 1991). Here, carrying the A1 allele was associated with higher reward sensitivity (Lee et al., 2007). Although Samachowiec and colleagues found no relation of the DA transporter (DAT) gene to the main *RewD* scale, carriers of the A9 allele showed lower scores in one *RewD* subscale, i.e. *dependence* (Samochowiec et al., 2001). One recent PET study, that sought to link placebo-effects to dopaminergic NAcc activity, found a difference in placebo-induced NAcc activation for high compared to low responders based on the subjects' individual perception of the current placebo efficacy (Scott et al., 2007). Furthermore, the authors of another PET study reported significant correlations between *RewD* scores and the opioid receptor binding potential within human ventral striatum (Klega et al., 2007). Another

study using glucose-metabolism PET demonstrated a positive relationship between *RewD* scores and metabolism in the caudate nucleus, a region that has been associated with reward processing (Hakamata et al., 2006). These findings provide an indirect hint for inter-individual differences in the prediction and evaluation of rewards. Interestingly, a norepinephrine challenge test revealed no significant correlation with *RewD* putting the hypothesized relationship between *RewD* and norepinephrine by Cloninger into question (Hansenne et al., 2002).

Taken together the findings suggest that *RewD* or reward sensitivity might develop under the influence of different biological and environmental conditions and can not be exclusively linked to alterations within one neurotransmitter system.

1.5. Aims of the thesis

1.5.1. Stimulus novelty and reward prediction

Given the strong evidence that both novelty and reward processing critically involve the dopaminergic system and share in part a common pathway with regard to behavioral modulation and hippocampal memory formation, one aim of this thesis is to clarify the potential interaction of both constructs when they are combined in one fMRI paradigm (experiments 1 and 2). To our knowledge, there is no study investigating the direct interaction of reward prediction and stimulus novelty in humans so far. It is hypothesized, that novelty/familiarity information that is added to reward-predicting cues will modulate the mesolimbic reward anticipation response in the sense of an exploration bonus. Novelty should thus enhance the reward-predicting properties of stimuli and by doing so should reduce neural responses at the time the reward is actually received. If stimulus novelty acts as an exploration bonus, it should influence not only working but also long-term memory. Furthermore, the influence of implicit versus explicit processing of reward-related stimulus properties during encoding will be investigated (experiment 1 versus 2).

1.5.2. Inter-individual differences

In order to investigate the influence of inter-individual differences in the processing of reward and novelty, the data of experiments 1 and 2 will be examined with regard to *NovS* and *RewD* scores as assessed via Cloninger's TCI. With respect to the evidence for a rather hard-wired DA-related *NovS* behavior, it is likely that inter-individual differences are reflected in alterations of the mesolimbic BOLD signal and later memory performance. Although several studies on reward provide evidence for alterations in brain activity based on inter-individual differences in *RewD*, the link to specific neurotransmitter systems still remains unclear. With regard to the current paradigm it is assumed, that alterations in *RewD* might affect the mesolimbic reward anticipation response.

1.5.3. DA transmission in rewarded tasks

The last aim of the present work refers to the relationship between different imaging methods used to acquire the reward anticipation response and the attempt to link it to dopaminergic neurotransmission. Although activations in fMRI paradigms and increased DA release as assessed via PET during rewarded tasks have been relatively well investigated, the direct relationship between the mesolimbic BOLD signal and striatal tracer displacement by DA still remains to be demonstrated. Thus, we sought to provide evidence for a correlation between striatal DA release and the BOLD signal within SN/VTA and NAcc during rewarded sessions in a combined PET/fMRI study (experiment 3a and 3b). Since there is no measurable PET signal within midbrain structures and no established evidence for a striatal DA-related novelty signal, the combined PET/fMRI study is restricted to the reward construct.

2. General Methods

All participants had been recruited for paid participation from the community of the Otto-von-Guericke-University Magdeburg and gave written informed consent to participate. fMRI experiments (i.e. experiments 1, 2 and 3b) were performed in Magdeburg in accordance with the Ethics Committee of the University of Magdeburg, Faculty of Medicine. Experiment 3a, including tracer synthesis, PET recordings, and structural MRI, was carried out at the Institute of Medicine at the Research Center in Jülich, with our main collaborators L. Minuzzi, D. Elmenhorst, M. Lang, and A. Bauer. The PET protocol had been approved by the Ethics Committee of the Medical Faculty of the Heinrich-Heine-University Düsseldorf as well as the German Federal Institute for Drugs and Medical Devices and the German Federal Office of Radiation Protection. The payment for PET scans was partly borne by the Institute of Medicine at the Research Center Jülich.

2.1. Visual stimulation

Colored photographs of complex natural and cultural every-day scenes served as cue pictures in all reported experiments. The stimulus set consisted of indoor and outdoor scenes and their assignment to the reward-predicting or neutral category was counterbalanced across subjects in all experiments. To prevent reinforcement effects due to personal reference or high salience, local or historic sights were excluded as well as identifiable persons or highly eye-catching details. All pictures had comparable spatial frequency values and were equalized regarding luminance differences. Within the scanning sessions, pictures and task were presented on a grey background in order to avoid blinding effects within the scanner.

2.2. Functional Magnetic Resonance Imaging (fMRI)

fMRI is a non-invasive imaging technique that utilizes the magnetic properties of blood and more precisely the ratio of oxy- to deoxyhaemoglobin denoted as

the Blood Oxygen Level Dependent (BOLD) contrast within the blood vessels as a measure of brain activity (Ogawa et al., 1993). The basis of the magnetic resonance is the so called 'spin' of atomic nuclei (such as hydrogen), which can be aligned to or oriented against an applied magnetic field and thus can have a low or high energetic state, respectively. During the acquisition of fMRI scans, a static magnetic field provides an aligned orientation of the hydrogen spins before a transversal radio wave is induced which causes a deflection of the axes and the phase of the nucleic spins. The measurable parameters are the result of the time the spins need to return to the orderly state determined by the static magnetic field after the transversal wave is turned off again. These parameters depend on the current oxygenation of the blood.

The most obvious advantage of the MRI method is the high spatial resolution without having any negative effect on the subject. Anatomical regions can be precisely distinguished and the functional event-related analysis allows for comparisons between different conditions with regard to specific cognitive processes. Since the BOLD response to one stimulus might last for more than 12 sec after stimulus onset (Matthews, 2001), one limiting factor in fMRI is the low temporal resolution compared to electrophysiological measures like Electroencephalography (EEG) or Magnetoencephalography (MEG).

2.3. Positron Emission Tomography (PET)

PET is another non-invasive imaging technique which can be used to quantify information on neurotransmission of specified biomarkers and receptor distributions within the human brain. In contrast to fMRI, a so called 'tracer' (radioligand) labelled with a radioactive nuclide of short half-life (such as ^{11}C) is injected to visualize brain activity. Different approaches investigate brain processes by means of specific receptor binding, glucose metabolism, or blood-flow. During the decay of the nucleotide, the emitted positron travels through the tissue and collides with an electron within 1 to 2 mm. Two gamma photons emerge as a product of this collision and are emitted in a 180 angle and can be recorded via coincidence detector-rings (consisting of crystal cores) near to the subject's head. The recording of two correspondent photons at the

same time is denoted as a coincident event that allows tracing back to the reference point in the tissue, yielding a detailed image of the tracer distribution in the brain. The tracer we employed during the PET measurements in experiment 3a was [^{11}C]raclopride, a selective D2 receptor agonist, that competes with DA on dopaminergic binding sites in the striatum and other cortical areas (Wagner et al., 1983). The parameter of interest is the change in receptor binding potential (BP) of [^{11}C]raclopride that provides an indirect estimation of actual DA release.

From a technical perspective, temporal resolution of PET is limited by the travelling-time of the emitted positron before collision, and the so called 'dead time', in which the detectors are refractory and not able to record arriving radiation. Moreover, the slow kinetics of tracer metabolism only allow for block-desings, limiting temporal resolution further.

3. Experiment 1

3.1. Introduction

The results of several recent studies on reward anticipation and novelty encoding implicate, that their might be a certain overlap of both processes with regard to the involved anatomical regions and the potential biological function of both stimulus features. This hypothetical interaction between novelty and reward processing might be due to an evolutionary pattern that drives animals to search for new sources of food or new territories. In sense of such a pattern, a new stimulus catches the attention of the observer by some kind of salience – which could be for example an anticipated reward or the appearance of a promising novel object or environment. The first interest of the observer depends on the specific features of the object or situation in sense of learned rewarding or in other sense promising details. Given that the first consideration captures the observer's attention and leads to approach rather than to withdrawal behavior, the actual value of the object or situation will be evaluated subsequently. Thus, novel stimuli that hold any familiar properties might raise the attention and curiosity, whereas completely unknown stimuli, that appear strange, very huge or loud, might cause feelings of fear or anger.

The present paradigm uses novel but natural and common pictures, that won't induce strong negative emotions like fear, disgust or anger – so we are able to focus on the basic effects of novelty in a rather familiar context. We decided for natural scenes in contrast to other paradigms on reward using objects because we suggest that natural novel environments might hold an exploration bonus that motivates the observer to further exploration (Kakade and Dayan, 2002). Another important issue has to be discussed with regard to this mechanism that is the individual psychological constitution. A subject with a rather passive or even fearful character might react in a completely different manner than an active or even impulsive person (Cloninger et al., 1998). Taken this together, it can be assumed that the response to novel objects or situations strongly depends on the stimulus features on the one hand and on personality features of the subject on the other hand.

3.2. Methods

3.2.1. Subjects and paradigm

24 young healthy volunteers (mean age ± standard deviation SD: 23 ± 1.7, 12 female) participated in experiment 1 (Exp 1). In order to investigate the potential interaction between novelty and reward, we conducted a 2*2 factorial event-related design, in which the factors *novelty* (novel versus familiar) and *reward* (reward-predicting versus neutral) were manipulated separately, resulting in the following experimental conditions: novel reward-predicting, familiar reward-predicting, novel neutral and familiar neutral. Subjects participated on 3 subsequent experimental days at the same day time. The interval of 24 hours was chosen to control for primacy and recency effects regarding memory performance and to allow for approximately similar conditions with regard to the subject's hormonal state and vigilance.

3.2.1.1. Familiarization phase

24 hours prior to the actual fMRI experiment, subjects were familiarized with one half of all picture stimuli on a standard office PC. 108 pictures were repeatedly presented within four blocks, resulting in each picture being shown six times for 2000 ms. Intermixed with these stimuli, 56 pictures (denoted as *distractors*) were presented once and not included in the actual scan session on the following day. 50% of all stimuli and distractor pictures were indoor scenes and 50% were outdoor scenes. Subjects were asked to indicate via button press whether they recognized the current picture or not.

3.2.1.2. Incentive task

The fMRI scans were acquired on the second day. Prior to the actual scanning, subjects performed a short training session on a standard PC outside the scanner to get familiarized with the task. The session was also intended to establish a robust cue-reward association to minimize learning effects during scanning and to obtain subjects' individual response deadlines in the number comparison task (see below).

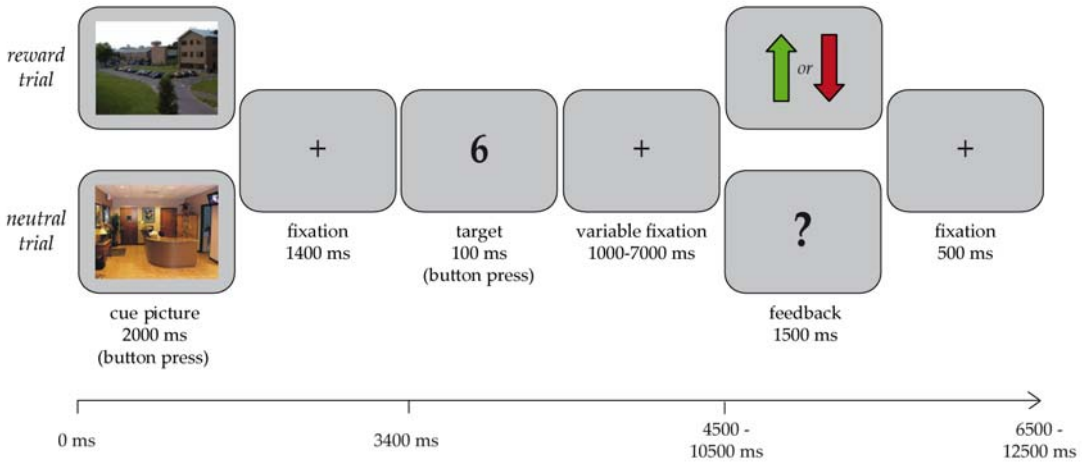


Fig. 3. Trial sequence for Exp 1. Trials started either with a reward-predicting or a neutral cue (indoor or outdoor scenes). Subjects were asked to indicate whether they had already seen the current cue picture the day before or not. Depending on their performance in the following number comparison task, subjects received a positive or negative feedback in rewarded trials. In neutral trials, the feedback arrows were replaced by a questionmark independent of the subjects' performance.

At the beginning of each trial, subjects saw a colored photograph of an indoor or outdoor scene for 2000 ms that served as a cue picture indicating the possibility for a reward or the absence of a reward with regard to performance in the following number comparison task, respectively (Fig. 3). For half of the subjects outdoor scenes served as reward-predicting cues, for the other half indoor scenes. Subjects were told that they could win money - or lose a smaller amount if they responded incorrectly or to slowly - in half of the trials (denoted as *rewarded trials*) whereas the other half of the trials would not influence their total gain (denoted as *neutral* trials). Subjects were asked to decide for each cue picture, if they had already seen it during the familiarization phase on the day before or if it was a completely novel picture. The reward information carried by the picture category thus remained implicit, whereas the novelty/familiarity information had to be actively represented during decision phase. Responses in the scanner were carried out on a response device box with the right index finger indicating 'familiar' and the right middle finger indicating 'novel' cues. Each cue picture was followed by a simple number comparison task (Pappata et al., 2002), in which subjects had to respond to a briefly flashed number (100 ms) ranging from 1 to 9 (except 5). Subjects were asked to press the left button for numbers below 5 and the right button for

numbers over 5 within a certain time window (Wittmann et al., 2005). In case of a correct and fast response to the number in rewarded trials, a green arrow pointing upwards was displayed on the screen as positive feedback for 1500 ms, indicating a gain of 50 ct in the current trial. Whenever the response in rewarded trials was incorrect or too slow, subjects received a red arrow pointing downwards as negative feedback, indicating a loss of 20 ct. In neutral (non-rewarded) trials a question mark replaced the arrow and served as a neutral feedback, regardless of the correctness of the response. In order to obtain comparable hit rates across subjects, the response time window for the incentive task was obtained during the training phase prior to scanning, and was subsequently adjusted automatically for every new trial based on the preceding individual subject's performance and response time. This dynamical adjustment led to a mean hit rate of approximately 75 % and thus, we ensured that each subject received positive feedback in the majority of trials. The feedback delay was jittered between 1 and 6 sec in order to separate overlapping BOLD responses elicited by reward anticipation and reward outcome, respectively. Thus, the total trial length varied between 6 and 12 sec and the fixation period between trials was 500 ms. Each subject performed three runs at 14 min consisting of 72 trials per run, yielding 18 trials per condition. Conditions were pseudo-randomised within each run in order to have at least 3 but maximal 6 trials of the same condition in a row. In addition, four fixation periods varying between 24 and 54 sec were included at randomly selected time points in each run to allow for a proper baseline estimation. Thus, subjects performed 108 rewarded and 108 neutral trials in total and each of these categories included 50 % familiar and 50 % novel pictures. The novelty/familiarity decision is important to control for the subject's ability to distinguish the majority of familiar and novel cues correctly and thus should assure the experimental manipulation of novelty and reward as equivalent factors.

3.2.1.3. Delayed memory test

24 hours after the fMRI session, a delayed memory test was performed on a standard office PC, including all 108 familiar and 108 novel stimuli of the

incentive task and 108 additional previously unseen distractor images. Each picture was displayed for 3000 ms and subjects were asked to indicate via button press, whether a picture belonged to one of the following three categories: 1= seen on the first as well as the second day (referred to as *familiar* cues); 2= seen exclusively on the second day (referred to as *novel* cues); 3= seen for the first time during the memory test (referred to as *distractor* items).

3.2.1.4. Personality questionnaire

In addition to the behavioral parameters and the fMRI data, subjects were handed out the Temperament and Character Inventory TCI (Cloninger et al., 1991) subsequent to the delayed memory test and were asked to send it back to the institute after completion at home. The main scales of interest regarding the current paradigm were *novelty seeking (NovS)*, especially the subscale *exploratory excitability (ExpE)*, *reward dependence (RewD)*, *harm avoidance (HarA)* and the correspondent subscales. For *reward dependence*, the alternative score *RewD*+ consisting of the subscales 1, 3 and 4 was taken into analysis providing an appropriate measure of *reward dependence,* since the second subscale (*persistence*) had been recognized as an independent factor in the revised version of the TCI (Cloninger, 1994). *ExpE*, the first *NovS* subscale, reflects the attention-related aspects of *NovS* and thus should fit best our paradigm on natural scene encoding (Tab. a1; a: Appendix A). All analyses that were carried out using the TCI had to be limited to 18 subjects that sent back the questionnaire and filled it in correctly (mean age ± SD: 23 ± 1.8, 9 female).

3.2.2. Data acquisition and analysis

3.2.2.1. fMRI acquisition

fMRI scanning was performed on a 3T Siemens Magnetom Trio MRI system (Siemens, Erlangen, Germany) at the University of Magdeburg. During study session on the second day, subjects performed three functional runs with 422 recorded volumes. 32 T2*weighted echo planar images (EPIs) were acquired for each volume in an axial slice orientation with a TR of 2000 ms and a TE of

30 ms (voxel size = 3.5*3.5*3.5 mm) using an interleaved scanning order starting from the bottom with even slice numbers first. Additionally, inversion-recovery EPIs (IR-EPIs) and structural proton density-weighted (PD) scans were obtained for anatomical localisation and coregistration.

3.2.2.2. Image processing and statistical analysis

fMRI data were preprocessed and statistically analyzed using SPM2 (Welcome Department of Imaging Neuroscience, Institute of Neurology, London, UK) and MATLAB 7.1 (The Mathwork, Inc.). Structural PD-weighted images were normalized to the template and averaged across subjects. We checked the registration of each single subjects' PD-weighted image on the PD template in order to control for an adequate midbrain normalization (see Appendix B). Functional images were realigned to the first functional volume in order to correct motion artifacts and spatially normalized to the standard EPI template provided by SPM2. Images were resliced to a final voxel size of 3*****3*****3 mm and smoothed with an isotropic 6 mm full-width half-maximum Gaussian kernel. Before model estimation, a high-pass filter of 128 sec was applied. Statistical analysis was conducted using a standard two-stage mixed-effects model. In the first stage, BOLD responses were modeled by delta functions time-locked to the onset of cue and feedback for all conditions of interest (*novel reward-predicting, familiar reward-predicting, novel neutral, familiar neutral*, plus a regressor containing the onset times of each target number), which were convolved with a canonical hemodynamic response function (HRF, Ashburner and Friston, 1999). The resulting time courses were downsampled for each scan to form covariates of a general linear model (GLM). Additionally, the six rigid-body-movement parameters determined from realignment (to capture residual movement-related effects) and a single constant representing the mean over scans were included as covariates of no interest. Parameters for each covariate were estimated by a least-squares fit to the data.

The second level of the analysis consisted of voxel-wise comparisons across subjects that were computed from the single subjects' contrast images, treating each subject as a random effect. More specifically, images of each contrast of interest on the canonical HRF were entered into two-tailed, one-

sample-t-tests. An a priori defined significance threshold of .005 (uncorrected, extent threshold k=5 adjacent voxels) was used as statistical cutoff for all voxel-wise comparisons if not denoted differentially. Coordinates of significant voxels were reported in a standard stereotaxic reference space (MNI, Montreal Neurological Institute).

In addition to the voxel-wise statistics, regions of interests (ROIs) were defined as spheres within ventral striatum (NAcc; 5 mm), medial midbrain (SN/VTA; 4 mm) and hippocampus (5 mm). Since the SN/VTA complex has a volume of about 350 to 400 mm^3 (Ahsan et al., 2007), 8 to 9 voxels can be comprised with the current resolution of 3.5*3.5*3.5 mm. Thus, there should be no resolution problems like it had been demonstrated in a recent study focusing exclusively on the VTA (D'Ardenne et al., 2008). The maxima of the HRF were extracted from these ROIs for each single subject and the mean signal change values of every condition within a time window of 2 sec surrounding the maximum of the individual subjects' BOLD responses were then tested by means of repeated measures ANOVAs (rANOVA) with factors *novelty* (novel versus familiar) and *reward* (reward-predicting versus neutral) – separately for reward anticipation and outcome phase.

3.2.2.3. Behavioral analysis

Response times (RTs) and hit rates were analyzed with regard to the cue encoding phase and the subsequent number comparison task separately. Regarding the delayed memory test, recollection performance was determined as correct classifications regarding the initial source day of encoding and corrected for false alarms within the corresponding category (referred to as *correct source* rate). Familiarity estimates were determined as incorrect classifications regarding the encoding source (referred to as *incorrect source* rate). In case of the former rewarded trials, only cues followed by positive feedback were included. All calculated response times, hit rates and recollection rates were than analyzed via rANOVA as described above.

3.2.2.4. TCI analysis

The scale and subscale scores were taken into correlational analysis to test for

inter-correlations among each other first. Correlations were then carried out between TCI scores *ExpE* and *RewD*+ and the BOLD signal change values during cue encoding of SN/VTA, NAcc and hippocampus. Furthermore, TCI scores were correlated with the recollection estimates of the delayed memory test.

3.3. Results

3.3.1. Behavioral data

3.3.1.1. Performance during cue encoding

Tab. 1 summarizes the subjects' performance in response to the presented cue. In the current experiment response rates and reaction times (RTs) refer to the novel/familiar decision. Familiar cue pictures were more often correctly classified when they were predicting reward (95 %) than when they served as neutral cues (91 %). For novel cue pictures correct rejection rate was lower for reward-predicting (83 %) than for neutral cues (88 %). A 2-way repeated measures ANOVA (rANOVA) with factors *novelty* (novel versus familiar) and *reward* (reward-predicting versus neutral) revealed a significant main effect of *novelty* ($F_{(1,23)}$=4.99, p=.036), while there was no main effect of *reward* (p-value >.6). Furthermore, performance for familiar cues was better when predicting reward, whereas for novel cues predicting reward performance was worse (interaction *novelty*reward* $F_{(1,23)}$=5.46, p=.029). For the RT-data novel reward-predicting cues yielded longer RTs than those for all other stimulus categories (see Fig. 4a). Performing a rANOVA analogous to the response rate analysis revealed significant main effects of *novelty* and *reward* accompanied by an interaction of both factors (*novelty* $F_{(1,23)}$=30.29, p=.000; *reward* $F_{(1,23)}$=6.54, p=.018*;* interaction *novelty*reward* $F_{(1,23)}$=14.92, p=.001).

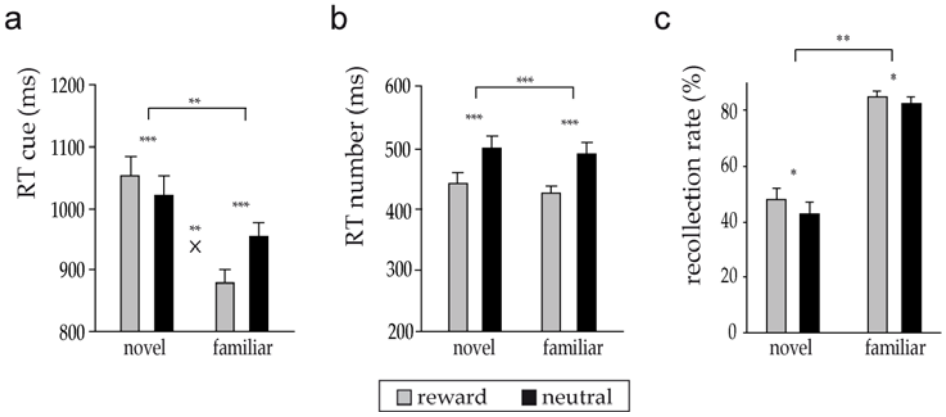


Fig. 4. Behavioral data of Exp 1. **(a)** RTs of the novelty/familiarity decision to the cue and **(b)** RTs of the number comparison task. **(c)** Recollection rates of the delayed memory test (error-bars depict standard error (SE); *p<.01, **p<.001, ***p<.0001).

3.3.1.2. Performance in the number comparison task

The analysis of hit rates regarding the number comparison task provides evidence that we adjusted the positive feedback rate in rewarded trials successfully to a mean around 75 %. When comparing the absolute (unadjusted) hit rates (see Tab. 1, Fig. 4b), the responses to the number targets were correct in at least 94 % of the trials and there was no significant differences between the four conditions (all p-values >.1). RTs to the number targets were significantly shorter after reward-predicting cues (main effect *reward* $F_{(1,23)}$=26.47, p=.000) and also shorter when the preceding cue was familiar compared to novels (main effect *novelty* $F_{(1,23)}$=20.35, p=.000).

3.3.1.3. Retrieval performance

In the delayed memory test on day three recollection memory was better for reward-predicting than for neutral cues and also better for familiar than for novel cues (Tab. 1, Fig. 4c). A rANOVA revealed significant main effects for both factors *novelty and reward*, but no significant interaction (*novelty* $F_{(1,23)}$=119.92, p=.000; *reward* $F_{(1,23)}$=4.82, p=.038; *novelty*reward* $F_{(1,23)}$=1.25, p=.276). For retrieval rates of familiar and novel cues subdivided into reward-predicting versus neutral, post hoc t-tests revealed a significant difference between reward-predicting and neutral novel cues (48 % vs. 43 % $T_{(23)}$=2.17, p=.041) but no significant difference for familiar cues (85 % vs. 83 % $T_{(23)}$=1.13, p=.271).

Tab. 1. Behavioral data of cue encoding, number comparison task, and memory test

	familiar cues		***novel cues***	
	rewarded	***neutral***	***rewarded***	***neutral***
cue encoding:				
response rate % (SD)	95 (6)	91 (10)	83 (18)	88 (15)
RT ms (SD)	879 (114)	954 (104)	1053 (157)	1020 (150)
number comparison task:				
response rate % (SD)	94 (6)	95 (6)	96 (4)	94 (7)
RT ms (SD)	426 (58)	485 (83)	440 (71)	493 (87)
delayed memory test:				
correct source % (SD)	85 (9)	83 (11)	48 (20)	43 (21)
incorrect source % (SD)	8 (9)	8 (9)	6 (7)	7 (5)

cue encoding: correct novel/familiar decisions
number comparison task: correct responses to the target number
correct source: correct classifications regarding the initial source day of encoding (corrected for false alarms)
incorrect source: incorrect classifications regarding the initial source day of encoding
SD: standard deviation

3.3.2. fMRI data

3.3.2.1. Reward anticipation phase

Analysis of the statistic parametric maps during presentation of the cue pictures revealed the expected prominent bilateral activation of the ventral striatum and the SN/VTA for reward-predicting relative to neutral cue pictures. Other reward-responsive regions were the anterior cingulate cortex (ACC), occipital cortex and hippocampal and parahippocampal regions (Tab. a2).

Cue novelty was mainly associated with strong activation in bilateral occipital regions (medial and lateral occipital cortex and fusiform gyrus), bilateral dorsal anterior cingulate cortex (dACC) and in a small cluster within bilateral hippocampus, while familiarity of cues led to a strong response within bilateral superior parietal lobe, bilateral medial prefrontal cortex (mPFC) and left lateral prefrontal cortex (lPFC; Tab. a3).

Familiar reward-predicting cues elicited the highest activation compared to all other stimulus categories within reward-related regions of the ventral striatum and the medial midbrain (Fig. 5a/b, Tab. a4).

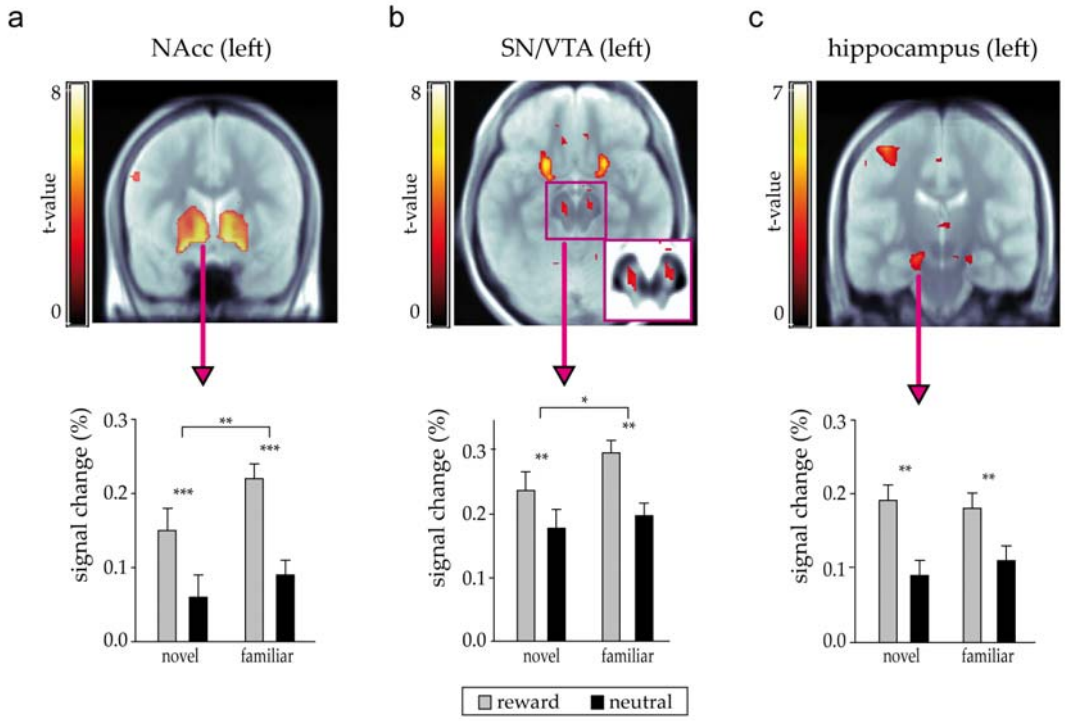


Fig. 5. Neural responses to reward-predicting cues in Exp 1. Activation within **(a)** NAcc (left x y z = -6 12 -9, T=6.44; right x y z = 9 9 -9, T=7.21), **(b)** SN/VTA (left x y z = -7 -18 -16, T=3.02; right x y z = 11 -17 -16, T=3.02) was strongest for *familiar reward-predicting* cues. **(c)** Hippocampal activity was enhanced for *reward-predicting* cues (left: x y z = -18 -19 -18, T=3.68). Activations are displayed on the PD-weighted anatomical images averaged across subjects with high contrast cut-out for SN/VTA. Bar plots depict estimated mean signal change of BOLD response within displayed ROIs for each experimental condition (error-bars depict SE; *p<.01, **p<.001, ***p<.0001).

A ROI-based rANOVA with factors *novelty* (novel versus familiar) and *reward* (rewarded versus neutral) of the mean BOLD signal change within the ventral striatum revealed significant main effects of both *reward* (left $F_{(1,23)}$=30.42, p=.000; right $F_{(1,23)}$=35.09, p=.000) and *novelty* (left $F_{(1,23)}$=10.74, p=.003; right $F_{(1,23)}$=12.97, p=.002) in bilateral NAcc but no interaction between the two factors (*novelty*reward* left $F_{(1,23)}$=1.60, p=.219; right $F_{(1,23)}$=.27, p=.610). Similar effects were observed in the ROI analyses within bilateral SN/VTA for *reward* (left $F_{(1,23)}$=11.27, p=.003; right $F_{(1,23)}$=5.54, p=.027) and for *novelty* (left $F_{(1,23)}$=7.2, p=.013; right $F_{(1,23)}$=6.8, p=.016) also in the absence of a significant interaction (p-values >.2). The corresponding ROI-analysis within hippocampus revealed a significant main effect of *reward* for signal change values in bilateral hippocampus (left $F_{(1,23)}$=14.54, p=.001; right $F_{(1,23)}$=10.04, p=.004; Fig. 5c) but neither a significant main effect for *novelty* nor an interaction (all p-values >.4).

3.3.2.2. Reward outcome phase

The feedback sequence of the trials could be separated into six categories depending on the preceding cue. These were novel reward-predicting stimuli followed by positive reward outcome (termed *novel-gained*) and the remaining categories *familiar-gained*, *novel-lost*, *familiar-lost*, *novel-neutral* and *familiar-neutral* feedback events. Since negative outcome was only given in 25% of the trials, we restricted the analysis to the positive feedback events.

Positive reward outcome was associated with activations in the bilateral anterior insula, the right ACC, fusiform gyrus, and in occipital regions, as well as in the right thalamus and right lPFC, irrespective of novelty/familiarity of the preceding cue (Tab. a5). After subdividing reward feedback as a function of novel versus familiar cues, positive feedback that was preceded by novel in contrast to familiar cues elicited significantly higher activations within ventral striatum, SN/VTA and right insula. In contrast, positive feedback that was preceded by familiar cues led to a different pattern with bilateral parahippocampal and occipital regions being more active. A ROI-based rANOVA of BOLD signal change revealed a significant main effect of *reward* ($F_{(1,23)}$=9.71, p=.005) and a tendency for interaction of *reward*novelty* ($F_{(1,23)}$=3.72, p=.066) within left NAcc. When applying post hoc t-tests, the

difference between outcome following novel reward-predicting and novel neutral cues was significant ($T_{(23)}$=3.70, p=.001), whereas no difference was found for familiar cues ($T_{(23)}$=.60, p=.554; see Fig. 5d).

3.4. Discussion

The results of Exp 1 are in line with earlier findings regarding the mesolimbic reward-anticipation response. Specifically, reward-predicting stimuli elicited a robust BOLD signal within medial midbrain and ventral striatum compared to neutral cues (Wittmann et al., 2005; Delgado, 2007). Furthermore, positive outcome was in general associated with a different activation pattern, including prefrontal and occipital areas. In the employed paradigm, reward in form of the given feedback is related to the subject's performance, in a way that subjects have to make an effort to receive the reward – in contrast to reward given by chance (like e.g. in the card guessing task). Thus, our data is comparable with several earlier studies (Knutson et al., 2001a; Kirsch et al., 2003; Knutson and Cooper, 2005; Wittmann et al., 2005) reporting a robust reward-anticipation response within medial midbrain and ventral striatum.

With regard to the novelty/familiarity of the stimuli, we found a modulation of the mesolimbic reward-anticipation response during explicit novelty/familiarity judgement. Novelty detection seems to abolish the reward-related responses in SN/VTA and NAcc during reward-anticipation, while the decision on familiar cues did not interfere with reward-processing. Furthermore, positive outcome following novel cues was accompanied by a striatal response to positive outcome in the feedback phase. We thus assume that explicit novelty detection is associated with higher processing effort compared to the recollection of familiar items, which was reflected in higher activation within dACC and visual processing areas. This observation was supported by the prolonged RTs to novel cues in the rewarded condition. The impeded decision regarding novel cues therefore led to a strong interference with reward-anticipation and to a temporal shift of the mesolimbic reward response towards the outcome phase (see Fig. 5).

With regard to later memory performance, the data provided further evidence for an enhancing effect of reward-prediction on long-term memory (Wittmann et al., 2005; Adcock et al., 2006). Interestingly, we found a higher reward-related memory gain for novel compared to familiar cues when subtracting the number of neutral from rewarded stimuli. This pattern perfectly reflects the alterations in the response to positive outcome.

These findings suggest that processing of stimulus novelty interferes with the processing of reward-predicting stimulus properties when attention is explicitly directed towards novelty. Another possible explanation would be that novelty per se captures attention implicitly, independent of the current task requirements. Experiment 2 tests this prediction by changing the task instruction so that subjects perform an explicit reward anticipation decision on the cue rendering novelty encoding implicit.

4. Experiment 2

4.1. Introduction

The unexpected outcome of Exp 1 on the behavioral level and with regard to fMRI data led us to the question, whether the interference of novelty detection and the ‘suppressed’ reward anticipation responses to novel stimuli might be due to the specific task instructions during cue encoding. The data of Exp 1 provides strong evidence for an impeded processing of novel cues carrying reward information, when novelty/familiarity is explicitly attended and a decision is executed.

In order to further investigate this phenomenon, we conducted a second experiment, in which we provided exactly the same information on the stimulus level, but modulated the task instructions to an explicit reward anticipation decision. The hit rates in the novelty/familiarity decision of Exp1 affirmed us of the subject’s ability to distinguish both cue categories properly, so that we could argue for leaving the novelty encoding being implicit in the second experiment. Thus, the current paradigm is similar to other studies, in which reward

anticipation is processed explicitly and requires a response (Wittmann et al., 2005). We expected a similar pattern with regard to the general reward information within ventral striatum and medial midbrain and an assimilated or even switched pattern regarding the reward anticipation of novel and familiar cues compared to Exp1.

4.2. Methods

4.2.1. Subjects and paradigm

22 young healthy volunteers participated in the second experiment. After exclusion of two subjects due to poor task performance, the data of 20 subjects was analyzed (mean age ± SD: 25 ± 2.9, 10 female). We used exactly the same 2*2 factorial event-related design like in the first experiment with the factors *novelty* (novel versus familiar) and *reward* (reward-predicting versus neutral) and the resulting four experimental conditions novel reward-predicting, familiar reward-predicting, novel neutral and familiar neutral. On the basis of the paradigm in Exp 1, the same stimulus set consisting of colored indoor and outdoor scenes was used and the new subjects completed the same familiarization phase on the first, the incentive task within the scanner on the second and the delayed memory test on the third day (for detailed description see section 3.2.1). The only difference compared to Exp 1 concerned the task instructions and response requirements for the cue picture. In contrast to Exp 1, subjects had to decide, if the current cue belonged to the rewarded or the neutral category. Thus, Exp 2 required explicit reward anticipation whereas novelty detection remained implicit, i.e. subjects were not asked to discriminate between novel and familiar pictures during cue encoding. The response was again carried out via button press with the right index finger referring to ‘reward predicting’ cues and with the right middle finger referring to ‘neutral’ cues. All analyses that were based on the TCI data had to be limited to 11 subjects that actually sent back the questionnaire and filled it in correctly (mean age ± SD: 26 ± 2.96, 5 female).

4.2.2. Data acquisition and analysis

The fMRI data acquisition and analysis was carried out in exactly the same way as in the first experiment (for detailed description see section 3.2.2.).

4.3. Results

4.3.1. Behavioral data

4.3.1.1. Performance during cue encoding

In the current experiment response rates and RTs refer to the reward/no-reward decision (explicit reward anticipation). Classification into reward-predicting and neutral cues was nearly perfect for all stimulus classes (see Tab. 2, Fig. 6a). Performing an analogous repeated measures ANOVA (rANOVA) to the behavioral analysis of Exp 1, RTs were found to be significantly shorter for reward-predicting compared to neutral cues (main effect *reward* $F_{(1,19)}$=17.47, p=.001) and also shorter for novel compared to familiar cues (main effect *novelty* $F_{(1,19)}$=5.25, p=.034). In contrast to Exp 1, there was no significant interaction between both factors (*novelty*reward* $F_{(1,19)}$=.45, p=.511).

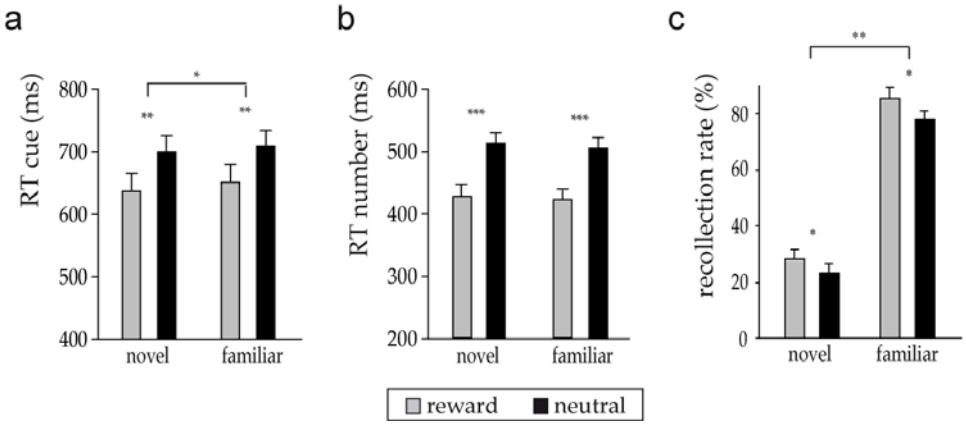


Fig. 6. Behavioral data of Exp 2. **(a)** RTs of the reward-anticipation response to the cue and **(b)** RTs of the number comparison task. (c) Recollection rates of the delayed memory test (error-bars depict SE; *p<.01, **p<.001, ***p<.0001).

4.3.1.2. Performance in the number comparison task

The adjustment of the hit rates guaranteed that subjects received positive feedback in 75 % of the rewarded trials. The absolute (unadjusted) hit rates for

the number targets were all above 96 % and no significant differences were observed between the four conditions (see Tab. 2, Fig. 6b). Regarding reaction times, we observed significant faster responses to the number targets when the preceding cue was reward-predicting ($F_{(1,19)}$=48.63, p=.000) but no significant differences after familiar compared to novel cues (p-values >.06).

4.3.1.3. Retrieval performance

Performance in the delayed memory task was again better for reward-predicting compared to neutral cues and better for familiar compared to novel cues (Tab. 2, Fig. 6c). The main effects of *novelty* and *reward* yielded by the rANOVA were significant and no interaction was found (*novelty* $F_{(1,19)}$=288.70, p=.000; *reward* $F_{(1,19)}$=4.38, p=.050; *novelty*reward* $F_{(1,19)}$=.38, p=.543). When performing post hoc t-tests on the retrieval data, we found a significant difference between reward-predicting and neutral familiar cues (86 % vs. 78 % $T_{(19)}$=2.25, p=.037) but no difference for novel cues (28 % vs. 23 % $T_{(19)}$=1.33, p=.200).

Tab. 2. Behavioral data of cue encoding, number comparison task, and memory test

	familiar cues		***novel cues***	
	rewarded	***neutral***	***rewarded***	***neutral***
cue encoding:				
response rate % (SD)	99 (1)	97 (4)	99 (2)	98 (4)
RT ms (SD)	652 (127)	706 (119)	638 (132)	699 (118)
number comparison task:				
response rate % (SD)	97 (3)	96 (4)	96 (4)	97 (3)
RT ms (SD)	424 (64)	506 (70)	431 (73)	514 (71)
delayed memory test:				
correct source % (SD)	86 (17)	78 (12)	28 (15)	23 (17)
incorrect source % (SD)	10 (12)	11 (10)	8 (9)	9 (8)

cue encoding: correct reward/neutral decisions
number comparison task: correct responses to the target number
correct source: correct classifications regarding the initial source day of encoding (corrected for false alarms)
incorrect source: incorrect classifications regarding the initial source day of encoding
SD: standard deviation

4.3.2. fMRI data

4.3.2.1. Reward anticipation phase

Analogous to Exp 1, we found a significant increase of the BOLD response for reward-predicting as compared to neutral cues within bilateral NAcc and SN/VTA as well as in bilateral ACC, occipital cortex, lPFC and right parahippocampal region (Tab. a6). In the second experiment familiar cues elicited a similar response pattern to Exp 1, that is, stronger activation of the bilateral superior parietal lobe and left lPFC when compared to novel stimuli. Novel stimuli, in turn, were now associated with stronger activation in bilateral insula, the medial midbrain (SN/VTA) and again in a small cluster within bilateral hippocampus when compared to familiar stimuli (Tab. a7).

In contrast to the first experiment, the highest reward-related activation in bilateral NAcc and SN/VTA was now elicited by novel rather than familiar reward-predicting cues (Fig. 7a/b, Tab. a9).

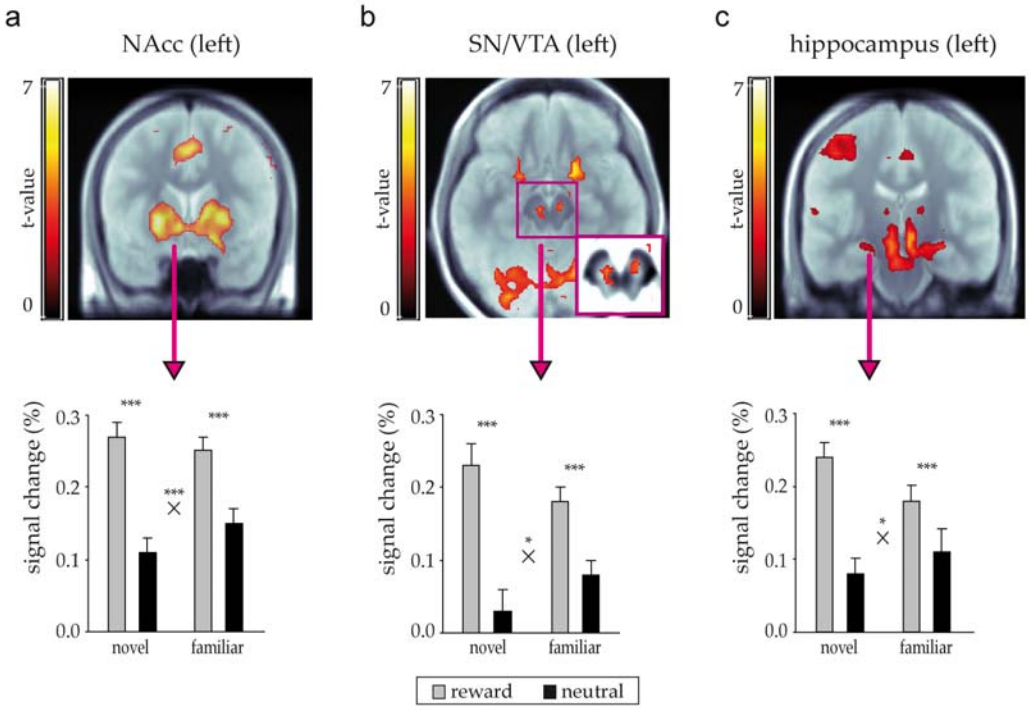


Fig. 7. Neural responses to reward-predicting cues in Exp 2. Activation within **(a)** NAcc (left x y z = -6 12 -6, T=5.61; right x y z = 18 15 -15; T=6.44) and **(b)** SN/VTA (left x y z = -6 -18 -17, T= 4.17; right x y z = 8 -17 -17, T=3.57) was strongest for *novel reward-predicting* cues. **(c)** Hippocampal activation was enhanced for *novel reward-predicting* cues (x y z = -24 -18 -15, T=2.16). Activations are displayed on the PD-weighted anatomical images averaged across subjects with high contrast cut-out for SN/VTA. Bar plots depict estimated mean signal change of BOLD response within displayed ROIs for each experimental condition (error-bars depict SE; *p<.01, **p<.001, ***p<.0001).

The rANOVA of the mean BOLD signal change revealed main effects of *reward* within bilateral NAcc (left $F_{(1,19)}$=48.05; p=.000; right $F_{(1,19)}$=69.61, p=.000) and bilateral SN/VTA (left $F_{(1,19)}$=53.24; p=.000; right $F_{(1,19)}$=36.5, p=.000). This main effect was accompanied by a significant interaction with *novelty* for bilateral NAcc (left $F_{(1,19)}$=13.69, p=.000; right $F_{(1,19)}$=8.66, p=.008) and the left SN/VTA ($F_{(1,19)}$=5.26, p=.033). The results of the ROI-based rANOVA within hippocampus displayed a significant main effect of *reward* for bilateral hippocampus (left $F_{(1,19)}$=25.86, p=.000; right $F_{(1,19)}$=14.64, p=.001) accompanied by a significant interaction of *reward* and *novelty* ($F_{(1,19)}$=7.49, p=.013) in the left hippocampus (Fig. 7c).

4.3.2.2. Reward outcome phase

Similar to Exp 1, positive reward outcome was associated with activations within bilateral anterior insula, right mPFC, right lPFC, right ACC, bilateral fusiform gyrus, occipital cortex and right thalamus (Tab. a9).

Notably, positive feedback preceded by familiar cues was associated with activations within ventral striatum, right SN/VTA and right parahippocampal region, whereas positive feedback following novel cues led to slightly stronger activations in bilateral thalamus and the occipital pole region. The ROI-based rANOVA of the mean BOLD signal change revealed a significant main effect of *reward* ($F_{(1,19)}$=6.54, p=.019) and a tendency for an effect of *novelty* ($F_{(1,19)}$=3.75, p=.068) within right NAcc. When applying post hoc t-tests, activation was significantly higher for positive outcome following familiar reward-predicting compared to familiar neutral cues ($T_{(19)}$=2.73, p=.013) but there was no significant difference for novel cues ($T_{(19)}$=.97, p=.342; see Fig. 7d).

4.4. Discussion

In line with the results of Exp 1 and the most part of comparable paradigms (for review see Delgado, 2007), the current data displayed a robust reward-anticipation response within SN/VTA and NAcc during the presentation of the

reward-predicting cue. In addition, the neural response to the reward outcome was located in comparable regions as in Exp 1.

However, the explicit processing of reward-related stimulus properties in the current paradigm led to a different influence of stimulus novelty. Here, stimulus novelty led to a robust enhancement of the reward-anticipation response, whereas the response for neutral novel cues was even diminished compared to familiar cues. Overall, subjects responded faster to novel compared to familiar cues during the explicit reward decision. In contrast to Exp 1, positive outcome following familiar cues was now associated with an striatal response to positive outcome (see Fig. 7).

In the delayed memory test, the reward-related memory enhancement for could be replicated for novel and familiar cues (Wittmann et al., 2005; Adcock et al., 2006). Importantly, in Exp 2 the reward-related memory effect was especially pronounced for familiar cues, providing a link to the reward outcome pattern for familiar cues analogous to the observations in Exp 1.

The assumption that stimulus novelty per se might be disadvantageous and impede reward processing (Exp 1) regardless of the task requirements could therefore not be supported by the second Exp. On the contrary, the current findings suggest, that stimulus novelty might hold an exploration bonus under conditions in which reward is explicitly attended (Kakade and Dayan, 2002), while novel stimuli lacking reward-related properties are not further explored or even blinded out in a way.

5. Meta-analysis experiments 1 and 2

Since we manipulated only on the level of task instructions and held the visual stimulation constant, we were able to analyze the data collapsed over both experiments. In order to investigate differences in Exp 1 and Exp 2 due to the task instructions, we compared RTs and retrieval rates by means of rANOVAs with *instruction* as between-subject-factor. fMRI data was analyzed by performing two-sample-t-test on the t-contrast maps of interest and ROI-based rANOVAs analogous to the behavioral data.

5.1. Differential pattern regarding behavioral data

5.1.1. Performance during cue encoding

The two experiments differed concerning the task that was performed during cue presentation. Therefore we performed a rANOVA on the response rates and RT data with factors *novelty* and *reward* additionally including the different task instructions as a between-subject factor (termed *instruction*). Response accuracy to the cue was significantly higher in Exp 2 over all cue categories due to the easier categorical reward/no-reward decision (three-way interaction *novelty*reward*instruction* $F_{(1,42)}$=4.19, p=.047). In addition, we observed significant interactions between *novelty* and *instruction* ($F_{(1,42)}$=4.50, p=.040), implicating a profound difference in task requirements between both experiments, as well as between *novelty* and *reward* ($F_{(1,42)}$=4.73, P=.035).

For RT data the analysis revealed significant main effects of *novelty* ($F_{(1,42)}$=20.26, p=.000) and *reward* ($F_{(1,42)}$=25.90, p=.000), accompanied by 2-way interactions with *instruction* (*novelty*instruction* $F_{(1,42)}$=28.89, p=.000; *reward*instruction* $F_{(1,42)}$=5.70, p=.022). In addition, we observed a significant interaction between *novelty* and *reward* ($F_{(1,42)}$=10.10, P=.003) and a significant three-way interaction between *novelty, reward,* and *instruction* ($F_{(1,42)}$=12.85, p=.001). In summary, the different task requirements led to significantly longer RTs to the cues in Exp 1 compared to the second experiment. Especially, responses to novel reward-predicting cues in Exp 1 were much longer compared to all other stimuli and longer compared to Exp 2. Conversely, RTs in

the second experiment displayed the inverted pattern with responses to novel reward-predicting cues being given significantly faster than those to all familiar and novel neutral cues. The prolonged RTs to novel cues in Exp 1 compared to Exp 2 support the hypothesis of a higher effort during the novelty/familiarity decision.

5.1.2. Performance in the number comparison task

Applying an analogous rANOVA on the response rates of the number comparison task, we observed a slightly higher accuracy in response rates to the target numbers in the second compared to the first experiment. This difference was reflected in a significant three-way interaction between *novelty, reward,* and *instruction* ($F_{(1,42)}$=5.18, p=.028). No other main effects or interactions were observed (all p-values >.7). Analyzing the RT data we found a main effect of novelty ($F_{(1,42)}$=20.45, p=.000) and a main effect of reward ($F_{(1,42)}$=73.0, p=.000). Thus, responses to target numbers in reward-predicting trials were given significantly faster compared to neutral trials and responses following familiar cues were slightly faster compared to novel cues over both experiments. In contrast to the responses during cue encoding, no significant interaction was found and thus the effects on RTs were independent of the given *instruction* (all p-values >.1). In summary, the results display a higher accuracy for target numbers in Exp 2, but the RTs in the number comparison task are not affected by the different task instructions during cue encoding.

5.1.3. Retrieval performance

An analogous analysis of the retrieval data comparing both experimental groups revealed the expected memory enhancement by reward across both experiments (main effect *reward* $F_{(1,42)}$=9.11, p=.004). Retrieval rates for familiar compared to novel cues were also significantly higher (main effect *novelty* $F_{(1,42)}$=374.49, p=.000). While retrieval rates for familiar stimuli were not substantially affected by different task instructions, retrieval rates for novel stimuli were substantially lower in Exp 2 compared to Exp 1, which is expressed in a significant interaction between *novelty* and *instruction* ($F_{(1,42)}$=13.20, p=.001). The three-way interaction between *novelty*, *reward* and

instruction was not significant ($F_{(1,42)}$=1.39, p=.249) and there were no significant interactions for *reward*instruction* and *novelty*reward* (p-values >.4). The lower recollection rates for novel cues in Exp 2 compared to Exp 1 can be regarded as a further hint for the higher encoding effort for novel cues in Exp 1 due to the explicit novelty/familiarity decision.

5.2. Differential pattern regarding fMRI activation

5.2.1. Mesolimbic reward processing

Exploration of the contrast maps of both experiments led to the assumption that the mesolimbic BOLD signal increase in response to novel reward-predicting cues might be stronger in Exp 2 compared to Exp 1. For a direct comparison between both experiments, a rANOVA over both experimental groups with *instruction* as additional between-subject factor was performed using the mean signal change values within ROIs in the ventral striatum (Fig. 8).

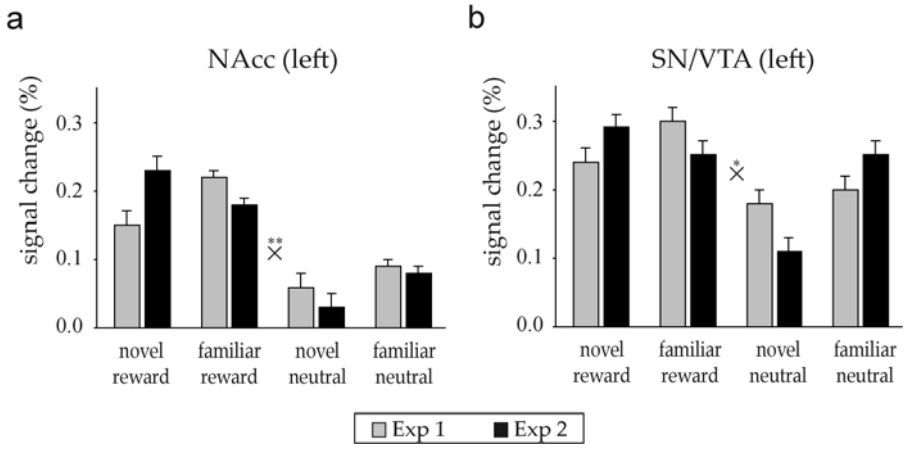


Fig. 8. Comparison of mean signal change during reward anticipation in Exp 1 and Exp 2. Bar plots depict estimated mean signal change of BOLD response in ROIs within NAcc **(a)** and SN/VTA **(b)**. The rANOVA including *instruction* as additional between-subject factor revealed a significant three-way-interaction of *novelty*reward* instruction* for both regions (error-bars depict SE; *p<.01, **p<.001).

The analysis within left NAcc revealed significant main effects of *novelty* ($F_{(1,42)}$=5.30, p=.026) and *reward* ($F_{(1,42)}$=77.86, p=.000), accompanied by a significant three-way-interaction with *instruction* (*novelty*reward*instruction* $F_{(1,42)}$=11.42, p=.002). A significant effect of *reward* was also observed in the

right NAcc ($F_{(1,42)}$=105.42, p=.000), accompanied by a significant interaction with *instruction* (*reward*instruction* $F_{(1,42)}$=6.56, p=.014) but not by a main effect of *novelty* ($F_{(1,42)}$=2.11; p=.154). Similar effects emerged from the analysis of reward-related regions in the medial midbrain. We observed significant main effects of *reward* ($F_{(1,42)}$=46.25, p=.000) and *novelty* ($F_{(1,42)}$=4.87, p=.033) for the left SN/VTA, again accompanied by a significant three-way-interaction (*novelty*reward*instruction* $F_{(1,42)}$=5.78, p=.021). The *reward* effect was also robust within the right SN/VTA ($F_{(1,42)}$=29.24, p=.000). Additionally, we observed an interaction between *novelty* and *instruction* ($F_{(1,42)}$=6.01, p=.018) and a tendency for the three-way-interaction (*novelty*reward*instruction* $F_{(1,42)}$=3.93, p=.054).

In order to investigate potential differences in the encoding of novel cues irrespective of their reward-predicting properties, two-sample-t-tests were carried out over the novelty contrasts (i.e. *novel versus familiar*) of both experimental groups. This analysis revealed activation clusters within the left dACC (see Fig. 9a) and bilateral lateral occipital cortex that showed a significantly higher BOLD response to novel stimuli in Exp 1 compared to Exp 2. In contrast, novel cues in Exp 2 were associated with significantly higher activation of the NAcc bilaterally, when compared to Exp 1 (see Fig. 9b).

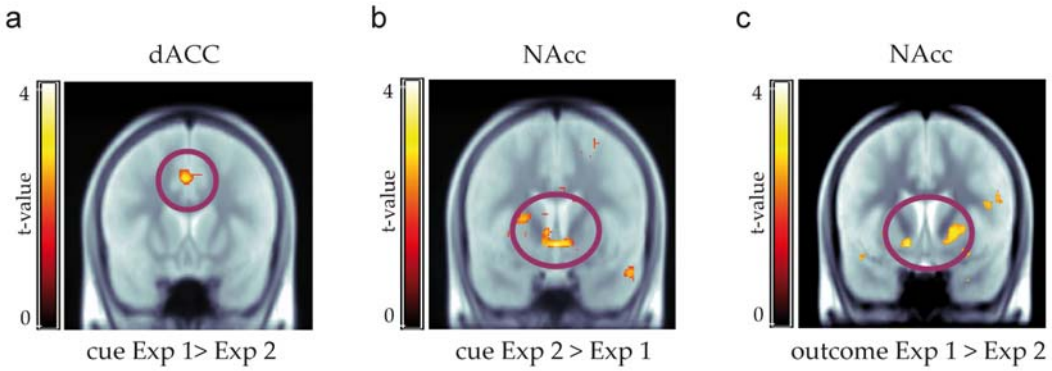


Fig. 9. Comparison between Exp 1 and 2 during cue encoding and positive reward outcome. **(a)** The two-sample-t-test of the contrast *novel vs. familiar* revealed significantly higher activations within bilateral dACC (left x y z = -3 15 39, T=3.03; right x y z = 7 23 39, T=2.54) in Exp 1 compared to Exp 2. **(b)** In contrast, in Exp 2 novel cues led to a stronger activation within bilateral NAcc (left x y z = -12 18 -9, T=2.70; right x y z = 9 18 -12, T=2.57). **(c)** During the outcome phase the contrast *novel-gain vs. familiar-gain* revealed significantly higher activations in bilateral NAcc in Exp 1, whereas the inverted contrast *familiar-gain vs. novel-gain* displayed higher activations in Exp 2 (NAcc left x y z = -12 9 -12, T=3.11; right x y z = 18 6 -9, T=3.34). Activations are displayed on the PD-weighted anatomical images averaged across subjects of both experiments (all p-values <.01).

5.2.2. Reward outcome and retrieval performance

One explanation for the relatively lower activation of the NAcc to reward-predicting cues in Exp 1 might be a less robust reward prediction, which would result in a larger subsequent response to reward outcome (Schultz, 2004; Schott et al., 2007). To test this hypothesis, we investigated the differences between both experimental groups in the reward outcome phase using two-sample-t-tests. In line with our hypothesis, the *novel-gain versus familiar-gain* contrasts yielded stronger mesolimbic activations in Exp 1 than in Exp 2 (Fig. 9c). A ROI-based rANOVA of the corresponding signal change values within NAcc over both groups with *instruction* as between-subject factor revealed a significant main effect of *reward* ($F_{(1,42)}$=15.94, p=.000), accompanied by a tendency for a three-way-interaction with *instruction* (*novelty*reward*instruction* $F_{(1,42)}$=3.16, p=.083). Notably, enhancement of retrieval performance for rewarded cues in the delayed recognition task (Tables 1 and 2) appeared to follow the pattern of the responses to reward outcome. Specifically, enhancement of retrieval performance by reward was more pronounced for novel cues in Exp 1 (hence paralleling the stronger responses to reward outcomes following novel as compared to familiar cues), as opposed by Exp 2 where a stronger enhancement was found for familiar cues (hence paralleling the stronger responses to reward outcomes following familiar as compared to novel cues). This suggests that the strength of responses to reward outcome might contribute to the reward-mediated enhancement of successful stimulus encoding.

5.3. Inter-Individual differences

In order to investigate inter-individual differences in reward and novelty processing, scores of two personality scales were analysed and related to the fMRI results and recollection performance. Novelty seeking and reward dependence were assessed using the TCI (Cloninger, 1991), with a focus on exploratory excitability (*ExpE*) and a representative score for reward dependence (*RewD*+). Given that the questionnaire data of experiments one and two should reflect trait characteristics that do not vary as a function of task

instructions, we included all 29 subjects into one correlational analysis (N_{Exp1}=18, N_{Exp2}=11; mean age ± SD: 24 ± 2.7, 13 female).

5.3.1. Scale inter-correlations

The scale inter-correlations of all 29 subjects are depicted in Tab. 3. All subscales were positively related to their correspondent parent scale. The strong positive relationship of novelty seeking (*NovS*) and the subscale *ExpE* provides evidence that the first subscale is a representative estimate of the core concept of novelty seeking and allows for further analysis based on this subscale. A similar relationship could be observed between reward dependence (*RewD*) and reward dependence+ (*RewD+*). The inverse correlation between *NovS* and harm avoidance (*HarA*) is compatible with common personality trait concepts and thus supports the validity of the scales. The hypothetical overlap between the reward and novelty concept is reflected in the positive relationship between *RewD* and *exploratory excitability (ExpE)*.

Tab. 3. Inter-correlations of TCI-scales of interest (n=29)

	RewD	***RewD+***	***NovS***	***ExpE***
RewD	r=1			
RewD+	r=.91** (p=.000)	r=1		
NovS	--	--	r=1	
ExpE	r=.49** (p=.007)	--	r=.77** (p=.000)	r=1
HarmA	--	--	r=-.47** (p= .009)	r=-.36* (p= .049)

RewD: reward dependence; *RewD+*: *RewD* subscales 1,3,4
NovS: novelty seeking; *ExpE:* exploratory excitability (subscale *NovS*)
HarmA: harm avoidance
** p<0.01 (two-tailed)
* p<0.05 (two-tailed)

Time-locked to the cue encoding phase, the mean BOLD signal change for each experimental condition (novel-rewarded, novel-neutral, familiar-rewarded, familiar-neutral) was extracted in defined ROIs in SN/VTA, NAcc, and hippocampus. In addition to the ROI-based analysis, recollection rates of the delayed memory test were calculated as correct classifications regarding source memory, namely the day of encoding. Here, only correlations between TCI scores (*ExpE/RewD+*) and BOLD responses in the three defined ROIs and

recollection rates are reported. To correct for multiple comparisons between TCI scores and BOLD responses, we introduced a Bonferroni correction (ROI(3)*stimulus(4)*hemisphere(2); cut-off at p<.002, two-tailed). Correlations between TCI scores and recollection rate were corrected for two comparisons (cut-off at p<.025, two-tailed). For a detailed list of correlation coefficients and p-values see Tables a10 and a11. In order to exclude the effect of different task instructions in both experiments, we applied a multiple linear regression analysis with *instructions* as additional independent factor for all significant correlational coefficients. The analysis revealed no significant contribution of task instructions for the relationship between *ExpE* and *RewD+* and the SN/VTA BOLD signal as well as for the relationship between *ExpE* and recollection rate (all p-values >.1).

5.3.2. Novelty seeking and reward dependence

The correlational analysis of the TCI scores and fMRI data revealed a significant relationship between *ExpE* and the BOLD signal within SN/VTA (see Fig. 10d) in response to novel neutral cues (r=.56, p=.002; Fig. 10a). In contrast, there was no significant correlation between *ExpE* and BOLD responses within NAcc (all p-values >.2). Surprisingly, high *ExpE* scores were associated with low fMRI activity within right hippocampus for familiar reward-predicting cues (r=-.57, p=.001). An analogous analysis revealed a significant correlation between *RewD+* and the BOLD response within right SN/VTA during encoding of novel reward-predicting cues (r=.57, p=.001; Fig. 10b). *RewD+* was not related to the BOLD response within NAcc or hippocampus on the basis of the Bonferroni correction (all p-values >.004).

Furthermore, *ExpE* was related to the recollection performance in the delayed memory test (Fig. 10c). High scores in *ExpE* were associated with a small difference between reward-predicting and neutral novel cues (r=-.43, p=.021) implicating a low memory gain for novel cues through their reward-predicting properties (Tab. a11). This relationship was accompanied by a negative correlation between the SN/VTA BOLD response to novel neutral stimuli and the memory enhancement by reward (r=-.57, p=.001). Recollection

rates in the delayed memory test were not related to *RewD+* scores (all p-values >.05).

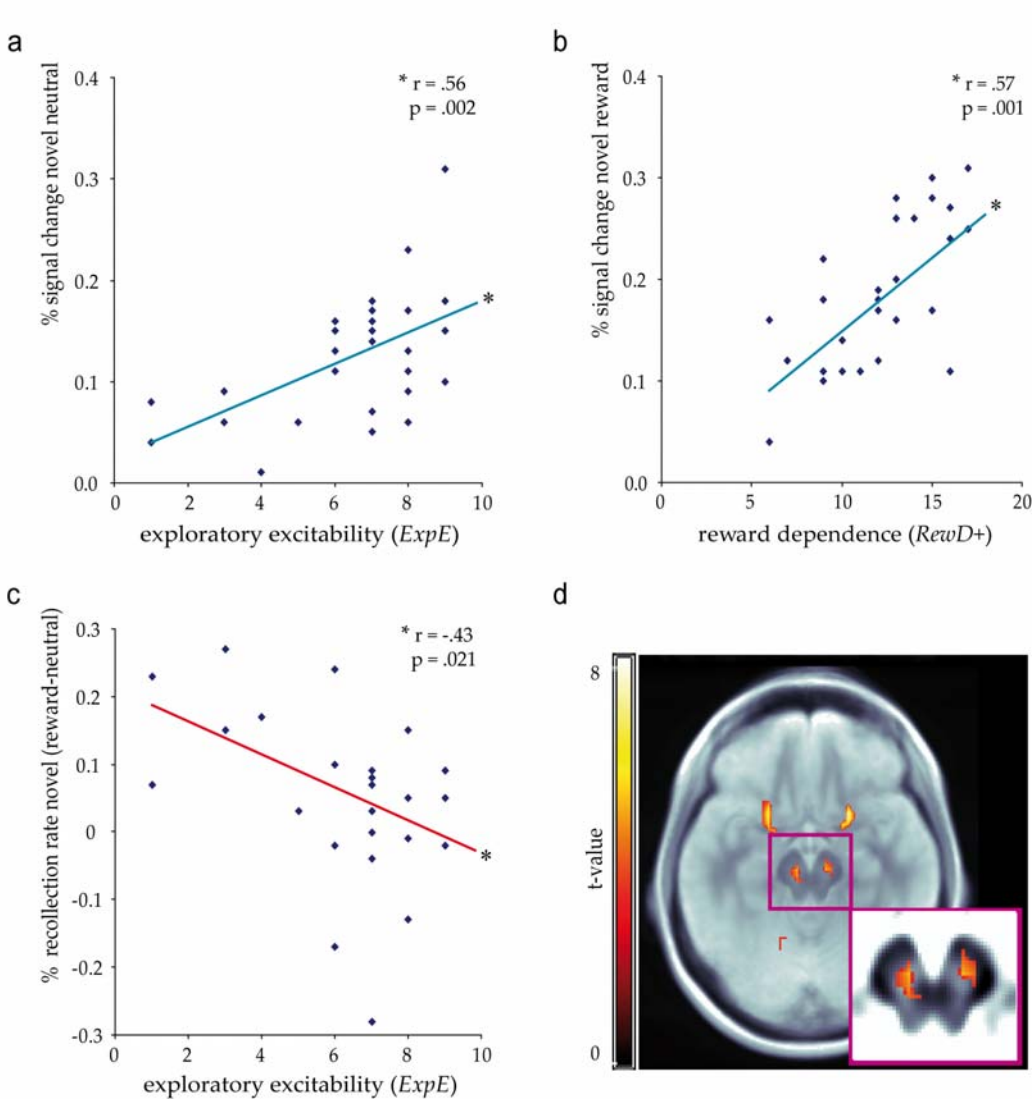


Fig. 10. Relationship between exploratory excitability (*ExpE*) / reward dependence (*RewD+*) and midbrain BOLD signal and retrieval performance. **(a)** *ExpE* is correlated with signal change during encoding of novel neutral cues (p<.002, two-tailed). **(b)** *RewD+* is correlated with signal change during encoding of novel reward-predicting cues (p<.002, two-tailed). **(c)** With regard to delayed memory performance, an inverse correlation could be observed between *ExpE* and the difference in recollection rate between novel-rewarded and novel-neutral cues (p<.025, two-tailed). **(d)** fMRI activation for novel reward-predicting cues is displayed on the PD-weighted anatomical images averaged across subjects with high contrast cut-out for SN/VTA (x y z = 9 -18 -18). Estimation of % signal change is based on a ROI-analysis in right SN/VTA.

6. Experiment 3

6.1. Introduction

Experiments 1 and 2, in line with earlier fMRI studies (Wittmann et al., 2005; Bunzeck and Duzel, 2006), report reward- and novelty-related activations of the midbrain (SN/VTA) and NAcc. These findings implicate an important contribution of DA within these processes. Consistently, PET studies that investigated the role of DA in reward-processing more directly, reported enhanced dopaminergic neurotransmission in the NAcc in the context of reward (Pappata et al., 2002; Zald et al., 2004). However, the direct relationship between neural activity within the mesolimbic system and actual striatal DA release still remains unclear. Several fMRI studies using pharmacological challenge tests in animals and humans suggest a positive relationship between striatal DA levels and the hemodynamic reward response (Knutson and Gibbs, 2007). A recent PET study on DA release during application of placebo displayed a positive correlation between individual striatal DA release and activation of the NAcc during a rewarded task (Scott et al., 2007), suggesting a relationship between striatal reactivity to reward and the individual capacity to release DA. However, the experimental situations in the two imaging modalities were not matched, and the analysis was restricted to the ventral striatum. As the DA-releasing neurons are located in the SN/VTA, activation within medial midbrain should show an even stronger correlation with DA-mediated ventral striatal [^{11}C]raclopride displacement during rewarded tasks.

In experiment 3 (Exp 3) we sought to directly investigate the relationship between reward-related striatal DA release measured via PET (Exp 3a) and the hemodynamic correlates of reward anticipation as assessed with fMRI (Exp 3b). Importantly, experimental conditions were kept virtually identical between the PET and the fMRI experiment, warranting a direct comparison between the results of these two measurement modalities. It was hypothesized that, across subjects, fMRI activation within SN/VTA and ventral striatum during reward anticipation would be positively correlated with the reduction of [^{11}C]raclopride

binding potential (BP) as an index of DA release during rewarded PET sessions.

6.2. Methods

6.2.1. Subjects and paradigm

Fourteen young healthy volunteers participated in the experiment (mean age ± SD : 22.8 ± 1.5, 6 female). Three subjects had to be excluded from analysis due to excessive movement in the PET study (two) and not complying with the task instructions (one). All subjects underwent routine clinical interview for neurological or psychiatric disorders. Exclusion criteria for participation were present or past neurological or psychiatric disease and the use of centrally acting drugs, including regular nicotine use (two subjects were light social smokers according to self report). Subjects were asked to avoid the intake of nicotine and alcohol for at least 24 and caffeine for at least 12 hours prior to the measurements. They were also instructed to get up in the morning at the same time on the days of the experiments to control diurnal variations in DA functioning.

Given the slow kinetics of [^{11}C]raclopride binding (Koepp et al., 1998), the task was divided into two sessions with the main conditions rewarded versus neutral (unrewarded) performed on two successive days. To allow for a better comparability of the fMRI and PET sessions, the fMRI study was also divided into two days, and the statistical model of the fMRI data analysis was matched to include the same proportion of rewarded/neutral trials in the PET data.

The same paradigm was used for both PET (Exp 3a) and fMRI (Exp 3b) experiments, with the session order and stimulus material counterbalanced across subjects. The only difference between PET and fMRI was that in both PET sessions, the stimulation was carried out for 36 min without interruption, while in both fMRI sessions the paradigm was split into three runs of 12 min each.

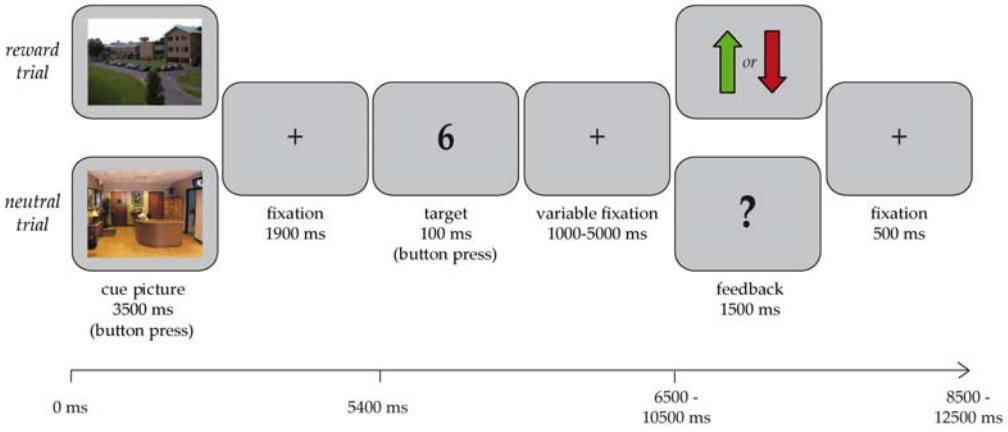


Fig. 11. Trial sequence for experiments 3a and 3b. The trial structure was taken from Exp 2 and differed only in the timing of the respective events to meet the requirements of PET measurements. Subjects had to indicate whether the current cue belonged to the reward-predicting or the neutral category, respectively.

The task was similar to the incentive task used in experiments one and two, except of slight timing differences. The trial timing for rewarded and neutral trials is depicted in Figure 11. Subjects saw a colored photograph of an indoor or outdoor scene for 3500 ms indicating that the following number comparison task includes the chance for a reward or no reward, respectively. For half of the subjects outdoor scenes served as reward-predicting cues, for the other half indoor scenes. In the rewarded session, 135 rewarded and 45 neutral trials were presented. Subjects were told that they could win money if they responded correctly and fast enough to the number or lose money if they responded incorrectly or too slowly in the rewarded trials, whereas the responses in the neutral trials would not influence their total gain. In the neutral session, 135 trials included neutral cues and 45 trials utilized cues of the rewarded category to keep the task constant over both sessions (indoor/outdoor judgment), but were in fact ‘unrewarded’. Subjects were explicitly told this, and were instructed to respond via button press whether they saw an indoor or outdoor scene. Each cue picture was followed by the same simple number comparison task as described in experiments one and two, in which subjects had to respond to a briefly flashed number (for details see section 3.2.1). To guarantee comparable hit rates, a dynamical adjustment was used analogous to experiments one and two yielding a mean hit rate of

approximately 75 % for each subject. In the rewarded trials of the actual reward session, subjects received an arrow pointing upwards or downwards after the task, indicating whether they won or lost money in the current trial. In contrast, in neutral trials of the rewarded session, as well as in all trials of the neutral session (independent of the cue category), a neutral feedback was displayed in the form of a questionmark. The feedback delay was jittered between 1 and 5 sec in order to separate the hemodynamic responses depending on reward anticipation and reward outcome, respectively. Thus, the total trial length varied between 8 and 12 sec. The fixation period between trials was 500 ms. Additionally, cued fixation periods of 16 sec were included at randomly selected time points to allow for an adequate baseline estimation in the fMRI study. To familiarize subjects with the cue-reward associations and reduce learning effects during the actual scanning, subjects completed a short training session before the actual experiment on each scanning day (all PET and fMRI scans).

6.2.2. PET data acquisition and analysis (Exp 3a)

6.2.2.1. PET acquisition

All PET scans were performed in 3D mode on a Siemens ECAT EXACT HR+ scanner (Siemens-CTI, Knoxville, TN, USA). The subjects were conducted to the PET scanner environment around one hour before the injection of the radioligand [^{11}C]raclopride (see Appendix C for radio-chemical synthesis). A training session lasting five min was applied before every scan. The subjects were subsequently placed in supine position with their heads being fixated by a vacuum pad. The position of the head was continuously monitored by a video system and reference skin marks, and manually corrected, if necessary. A venous catheter was placed in the subject's arm for the radioligand administration.

A 10-min 68Ge/68Ga transmission scan was acquired to correct for attenuation. A 60 min-long dynamic emission recording was initiated upon intravenous bolus injection of [^{11}C]raclopride over one min (mean injected radioactivity = 243.7 +/- 33.87 MBq in the rewarded, and 234.3 +/- 22.87 MBq in the neutral condition; $T_{(13)}$=.56, p=.586). PET data was acquired in list mode

and reframed into the dynamic sequence of 6*5 sec, 3*10 sec, 4*60 sec, 2*150 sec, 2*300 sec and 4*600 sec (Lammertsma and Hume, 1996).

In order to exclude abnormalities in the central nervous system and to allow for the coregistration of the anatomical data with the PET results, a high-resolution magnetic resonance imaging (MRI) was acquired from each subject using a Siemens 1.5T Magneton Vision scanner (Siemens, Erlangen, Germany) in a 3D T1-weighted magnetization-prepared rapid acquisition gradient-echo sequence.

6.2.2.2. Image processing and statistical analysis

Data sets were realigned manually to the anterior comissure/posterior comissure line using interactive three-dimensional image registration software (MPI-Tool version 3.35, ATV, Germany; (Pietrzyk et al., 1994). Summed PET recordings for each subject were manually coregistered to the individual realigned MRI data sets and the registration parameters were applied to each dynamic frame using the MPI-Tool software. ROIs defining caudate (total, lateral and medial), putamen (total, lateral and medial), NAcc and cerebellum were drawn onto the individual MRI images using PMOD software (PMOD, version 2.75, Zürich, Switzerland). BP was defined as the ratio of the specifically bound to the non-displaceable (BP_{ND}) radioligand in the tissue at equilibrium (Innis et al., 2007). Parametric maps of [^{11}C]raclopride BP_{ND} were calculated using the non-invasive method of Logan implemented in PMOD software, with the cerebellum as reference region (Logan et al., 1996).

Statistical analyses were performed using SPM2 and the MarsBaR ROI analysis tool (Brett et al., 2002). For voxel-based analysis, individual BP_{ND} parametric maps were initially smoothed with a Gaussian kernel of 3*3*3 mm and coregistered to the subjects' individual proton-density-weighted images (PD-weighted) acquired during the fMRI study (see Exp 3b). BP_{ND} maps were then normalized into a standard stereotaxic reference space (MNI, Montreal Neurological Institute), and smoothed using a Gaussian kernel of 6*6*6 mm. The striatum was segmented manually into caudate, putamen and NAcc bilaterally from a normalized (1*1*1 mm) and smoothed (3*3*3 mm) PD-weighted image of one subject, using the MRIcro image analysis software tool

(http://www.sph.s.c.edu/comd/rorden/mricro.html). Statistical analysis over the ROIs was performed using a two-sample t-test model, comparing the reward condition and the neutral condition for each subject. For the ROI-based analysis, the MarsBaR ROI analysis tool was used. The significance threshold for the ROI analysis was set to p=.05, Bonferroni-corrected for the number of ROIs. For voxel-wise analysis, the same statistical model was applied. Here, the significance threshold was set to p=.005, uncorrected, with a minimum of 15 adjacent voxels, and the analysis was restricted to the striatum.

6.2.3. fMRI data acquisition and analysis (Exp 3b)

6.2.3.1. fMRI acquisition

Both fMRI sessions were carried out on the 3T Siemens Magnetom Trio MRI system (Siemens, Erlangen, Germany) at the University of Magdeburg. Subjects performed three functional sessions on both fMRI-scanning days. 360 echo-planar images (EPIs) were acquired per run in an interleaved manner (32 axial slices; voxel size = 3.5*3.5*3.5 mm; TR=2000 ms; TE=30 ms; even numbers first). Additionally, a co-planar PD-weighted MR image was obtained and used for coregistration to improve spatial normalization.

6.2.3.2. Image processing and statistical analysis

As in the PET study, data analysis was performed using SPM2. EPIs from both scanning days were corrected for acquisition delay, realigned to the first image acquired, normalized to the MNI reference frame (voxel size = 2*2*2 mm) using the co-planar PD image to determine normalization parameters, and smoothed using a Gaussian kernel of 6*6*6 mm.

Statistical analysis was carried out using a two-stage mixed effects model as described above. In the first stage, the hemodynamic response was modelled by convolving a delta function at stimulus onset with a canonical HRF (Friston et al., 1998). The resulting time courses were then downsampled for each scan to form covariates of a GLM. The model included separate covariates for each of the conditions of interest, i.e. for the rewarded sessions (reward-predicting and neutral cues, feedback to correct and false responses to reward-predicting and neutral cues, respectively, and target numbers) and the

neutral sessions (neutral cues, cues that would be associated with reward during the rewarded sessions, neutral feedback to correct and false responses, respectively, and target numbers). The six rigid-body movement parameters determined from realignment were included in the GLM as covariates of no interest. Model estimation was performed using an ordinary least squares fit, and contrasts of parameter estimates were computed for the hemodynamic responses to reward anticipation.

In order to allow for a better comparability with the PET model (which compared sessions from two separate days), contrasts of the parameter estimates for reward anticipation included the reward cues (weighted +1) and the neutral cues (weighted -.25) from the rewarded condition, as well as the neutral cues in the neutral condition (weighted -.75). Previous studies had shown the possibility of between-session comparisons in fMRI, when the inclusion of fixation periods allows for a proper baseline estimation (Josephs and Henson, 1999; Schott et al., 2005). In the second stage of the model, these contrasts were submitted to a random-effects analysis, treating each subject as a random effect. Specifically, one-sample t-tests were computed over images of the reward anticipation contrasts. As in the PET study, the significance threshold was set to $p<.005$, uncorrected, with a minimum of 15 adjacent voxels.

6.2.4. Correlational methods comparing 3a and 3b

Given the assumption that reward-related DA release would be most prominent in the ventral striatum and that the PET results displayed the most reliable reward-related [^{11}C]raclopride displacement in the left NAcc, the relative decrease of tracer binding in this region was chosen as independent variable for a regression analysis. In order to investigate the relationship of reward-related [^{11}C]raclopride displacement and fMRI activation within medial midbrain and ventral striatum, we performed a ROI analyses in the left midbrain and left ventral striatum. The bilateral SN/VTA were segmented manually from a normalized and smoothed PD-weighted MR image of a study participant (see above). ROIs in the ventral striatum were selected individually for each subject by seeding a sphere (radius=6 mm) at the individual local maximum closest to

[x y z = -6 10 -69], where the PET analysis had shown the maximal radioligand displacement. The MarsBaR ROI analysis tool was used to compute a regression analysis over the midbrain and NAcc contrast values in the reward anticipation contrast, with [^{11}C]raclopride displacement in the left NAcc as independent variable. The significance threshold for the correlations was set to p=.05, one-tailed, as positive correlations with DA release were hypothesized.

Voxel-wise regression analysis was performed over the individual subjects' contrast maps derived from the SPM analysis, also using [^{11}C]raclopride displacement in the left NAcc as independent variable. As in all voxel-wise comparisons, the significance threshold was set to p=.005, uncorrected, with an extent threshold k=15 adjacent voxels.

6.3. Results

6.3.1. Behavioral results Exp 3a and 3b

6.3.1.1. Performance during cue encoding

Across both the PET study and the fMRI study, subjects reliably recognized reward cues and neutral cues (mean correct response rates > 92 % for all categories). Accuracy of responses was slightly higher in the rewarded relative to the neutral session, with lowest hit rate occurring for the 'reward' cues in the neutral session (92 % in fMRI and 93 % in PET). A three-way rANOVA over *modality* (PET vs. fMRI), *session type* (rewarded versus neutral session) and *reward* (reward-predicting versus neutral cues) revealed a main effect of *session type* ($F_{(1,10)}$=25.36, p=.001) and a *session type*reward* interaction ($F_{(1,10)}$=16.38, p=.002), but no effect of *modality* and no further interactions (all p-values >.1). Tab. 4 displays the RTs to cue pictures, separated by the factors *modality*, *session type* and *reward*. Reaction times were fastest for the reward-predicting cues in the rewarded session (three-way rANOVA *modality*session type*reward*: main effect of *session type* $F_{(1,10)}$=8.89, p=.014; interaction *session type*reward*: $F_{(1,10)}$=81.80, p<.001).

6.3.1.2. Performance in the number comparison task

In rewarded trials, subjects received positive feedback in around 75 % of the trials due to the individual adjustment of the response time window. Regarding the unadjusted response rates, subjects responded correctly to the target numbers in all conditions in at least 96 % of the trials. Similar to the cue responses, the RTs in the number task (Tab. 4) were shortest for rewarded trials in the rewarded session (three-way rANOVA *modality*session type*reward*: main effect of *session type* $F_{(1,10)}$=22.01, p=.001; main effect of *reward* $F_{(1,10)}$=81.47, p<.001; *session type*reward* interaction $F_{(1,10)}$=39.90, p<.001).

Because rare items (neutral cues in the rewarded session and 'reward' cues in the neutral session) were associated with longer reaction times, we computed post hoc paired t-tests over the RTs to reward cues and numbers from the reward session and the neutral cues and numbers from the neutral session, separately for PET and fMRI. In all cases, shorter RTs for the reward condition were observed (all $T_{(10)}$>2.05, all p<.034). Across sessions and conditions, reaction times were slightly longer in the PET experiment (cues: main effect of *modality*: $F_{(1,10)}$=28.96, p<.001; number targets: main effect of *modality*: $F_{(1,10)}$=54.94, p<.001), possibly due to the more distracting environment in the PET relative to the fMRI experiment.

Tab. 4. RTs for cue encoding and number comparison task

	reward session		***neutral session***	
	reward	***neutral***	***"reward"***	***neutral***
cue encoding:				
PET RT ms (SD)	694 (142)	766 (113)	808 (170)	775 (165)
fMRI RT ms (SD)	614 (120)	708 (110)	784 (181)	715 (137)
number comparison task:				
PET RT ms (SD)	454 (40)	501 (47)	516 (61)	513 (59)
fMRI RT ms (SD)	412 (30)	454 (46)	487 (61)	483 (59)

cue encoding: correct reward/neutral decisions
number comparison task: correct responses to the target number
SD: standard deviation

6.3.2. Reward-related [^{11}C]raclopride displacement in Exp 3a

Figure 12a (adapted from Schott et al.) depicts representative [^{11}C]raclopride binding potential curves for specific (ventral striatum) and non-specific (cerebellum) radioligand binding from a single study participant. Subjects showed a significantly decreased [^{11}C]raclopride BP_{ND} in the left ventral striatum during the rewarded session (i.e. 75 % rewarded trials) as compared to the neutral session (i.e. 100 % neutral trials), most likely resulting from ligand displacement by endogenous DA.

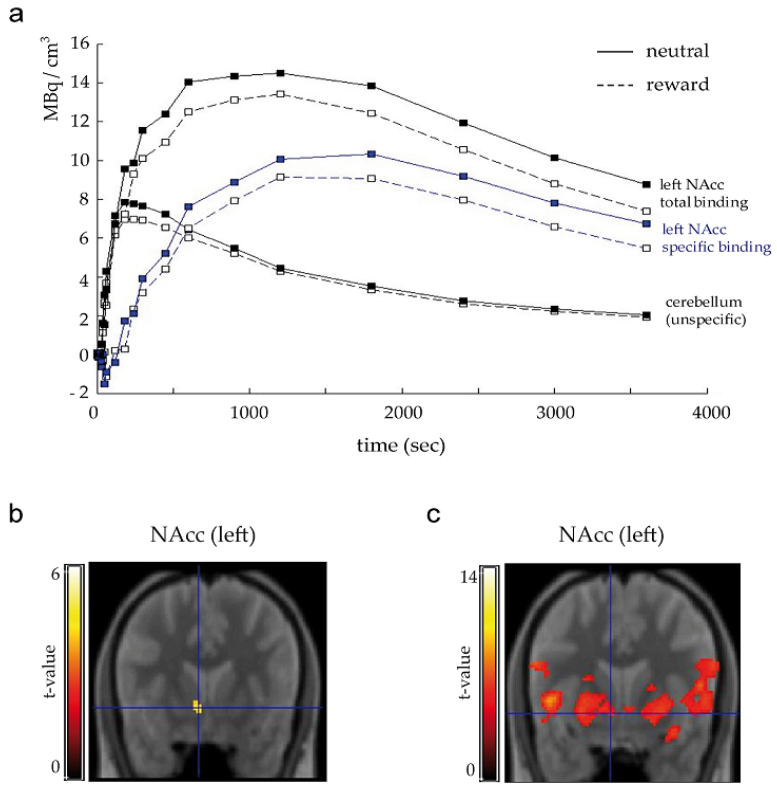


Fig. 12. (a) Time-activity curves of a representative subject, displaying the total binding in the NAcc, unspecific binding in the cerebellum, and specific binding in the NAcc as the difference in NAcc minus cerebellum are shown. Bottom panel: DA release and fMRI activations in the ventral striatum. **(b)** [^{11}C]raclopride displacement in the left NAcc (x y z = -6 10 -6) in rewarded compared to neutral sessions. **(c)** Activation of the ventral striatum (x y z = -8 6 -8) in the same contrast in the fMRI study.

A ROI-based analysis of striatal [^{11}C]raclopride BP_{ND} reduction revealed a robust BP_{ND} decrease in the left NAcc that remained significant after Bonferroni correction for the number of ROIs (Tab. 5). Voxel-wise t-test statistics confirmed this result by revealing a significant cluster of BP_{ND} reduction in the left NAcc (Fig. 12b adapted from Schott et al.).

Tab. 5. [^{11}C]raclopride displacement in the striatum

	BP_{ND} *decrease (SE)*	*Contrast*	*T*	*p*
NAcc				
left	**.17** (.08)	.08	2.86	.0084*
right	**.02** (.08)	.00	.00	.4986
Caudate				
left	**.04** (.05)	.03	1.03	.1646
right	**-.03** (.19)	-.03	-1.24	.8792
Putamen				
left	**.01** (.09)	.01	.23	.4098
right	**-.05** (.06)	-.00	-.08	.5309

BP_{ND} *decrease:* mean difference between the rewarded and the neutral session from the PMOD analysis
SE: standard error
Contrast,T, p: statistical results from the MarsBaR-based ROI analysis in SPM2
*the result in the left NAcc remained significant at p<.05 after Bonferroni correction for the number of ROIs

6.3.3. fMRI correlates of reward anticipation in Exp 3b

In order to allow for better comparability of the fMRI results to the PET results, the hemodynamic correlates of reward anticipation were compared with the responses to neutral cues taken from both days of scanning, weighted proportionally to the total number of cues (see section 6.2.3.2 for details). In line with previous studies, reward anticipation was associated with activation of an extensive mesolimbic network. Compared to neutral cues, reward-predicting cues were associated with an increased fMRI response within ventral striatum (Fig. 12c), to some extent dorsal striatum, insula, and medial midbrain. There was no activation in these regions in response to reward outcome (i.e. positive versus neutral feedback), as would be expected for young, healthy, participants when the stimulus-reward association has been well learned (Knutson et al., 2001b; Knutson and Cooper, 2005; Wittmann et al., 2005; Schott et al., 2007).

6.3.4. Correlational analysis of Exp 3a and 3b

To investigate how the hemodynamic reward anticipation response relates to reward-related DA release, a linear regression analysis of the DA BP_{ND} reduction in the left NAcc and the BOLD response during reward anticipation was computed. Based on previous studies (Adcock et al., 2006; Bunzeck and Düzel, 2006; Schott et al., 2006; Wittmann et al., 2005, 2007), in which midbrain activity that was likely to reflect the firing of dopaminergic neurons has typically been localized to the SN/VTA, we defined a ROI separately for the left and right hemisphere. Across the 11 subjects [^{11}C]raclopride displacement in the left NAcc showed a significant positive correlation with the hemodynamic

response of the left SN/VTA (r=.748, p=.004; Fig. 13a, adapted from Schott et al.). Regarding the right SN/VTA, there was also a positive correlation between BOLD response and [^{11}C]raclopride BP reduction within left NAcc, but failed to reach significance.

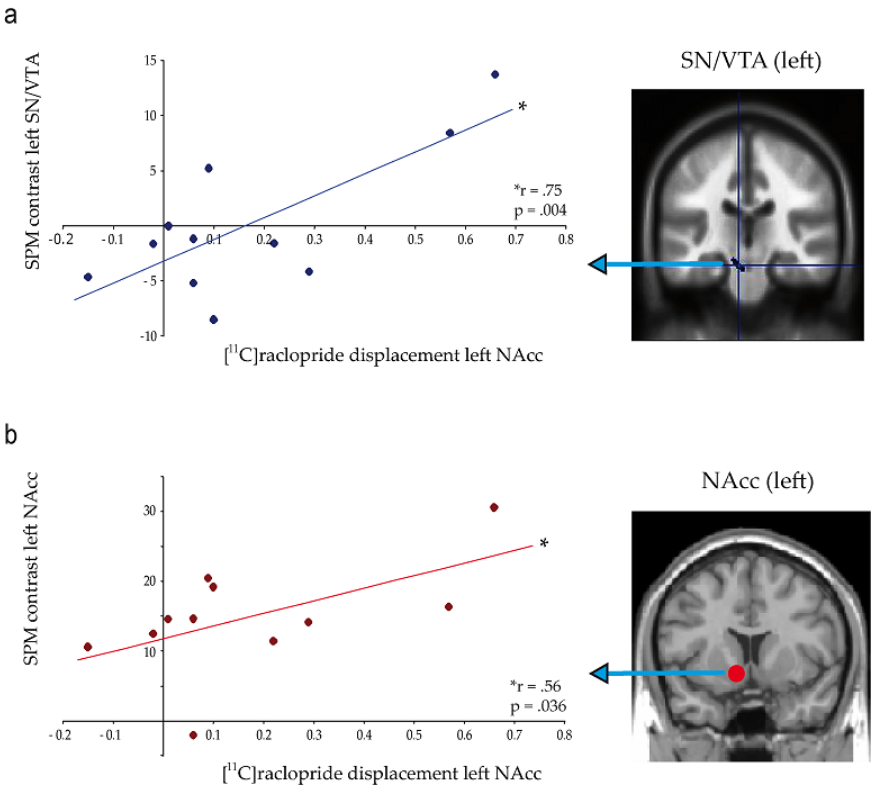


Fig. 13. Correlation of DA release and fMRI activations. **(a)** FMRI response in the left midbrain (depicted in blue; x y z = -7 -23 -18) during reward anticipation was significantly correlated with [^{11}C]raclopride displacement in the rewarded relative to the neutral condition. **(b)** A significant correlation was also observed between [^{11}C]raclopride displacement and the fMRI response in the left NAcc (depicted in red). Spheres of 6 mm were centered at each subject's individual local maximum of the reward anticipation response closest to 'x y z = -6 10 -6', the coordinate of maximal reward-related BP_{ND} decrease in PET.

It was further hypothesized that [^{11}C]raclopride displacement in the ventral striatum might correlate with fMRI activation of the same region. We therefore conducted a ROI analysis, using 6 mm spheres centered on the subjects' individual local maxima closest to [x y z = -6 10 -6], i.e. the voxel showing the maximal radioligand displacement in the PET data (see Fig. 12b). A linear regression analysis revealed a moderate, positive relationship between the BP_{ND} difference (neutral - rewarded) in the left NAcc and fMRI BOLD response

of the left NAcc during presentation of reward-predicting cues (r=.563, p=.036; Fig. 13b).

Voxel-wise linear regression analysis (p<.005, uncorrected, k=20 voxels) confirmed the result of the ROI-based statistics, revealing a significant positive correlation of [^{11}C]raclopride BP_{ND} reduction with BOLD activations in the left SN/VTA and in the left NAcc (Fig. 14). Additionally, we observed a positive correlation between NAcc [^{11}C]raclopride BP_{ND} decrease and the hemodynamic reward anticipation responses in the left amygdala and in the bilateral hippocampus as well as portions of the thalamus and dorsal striatum. The only brain region in which a negative correlation of the BOLD response to reward cues with [^{11}C]raclopride displacement was observed at the chosen statistical threshold was the left fusiform gyrus (x y z = -44 -46 -20).

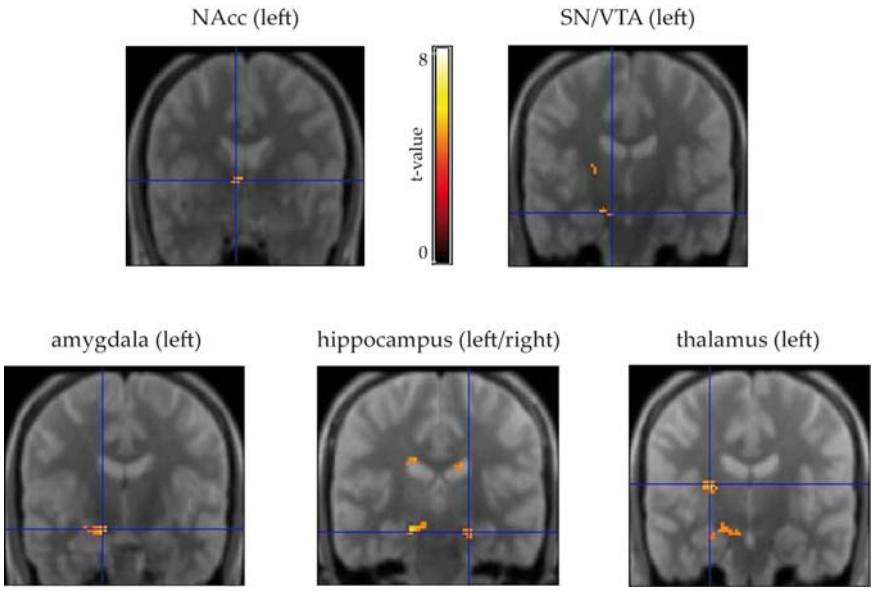


Fig. 14. Voxel-wise regression analysis over the single subjects' SPM contrasts (*reward-predicting vs. neutral*) with NAcc [^{11}C]raclopride displacement as regressor. As in the ROI analysis, activations in the left NAcc (x y z = -6 -4 2) and in the left SN/VTA (x y z = -10 -22 -18) correlated significantly with radioligand displacement in PET. Additionally, correlations with [^{11}C]raclopride displacement were also observed in the left amygdala (x y z = -26 -20 12), in bilateral hippocampus (x y z = 20 -28 -18), and in the left thalamus (x y z = -14 -14 -16).

6.4. Discussion

The results of Exp 3 provide evidence for an actual relationship between striatal DA release in a rewarded task and the mesolimbic BOLD response during reward anticipation in the same paradigm. Activations within SN/VTA, where dopaminergic neurons are housed, as well as within ventral striatum, a major target region of DA neurons, were positively correlated with DA release in the ventral striatum as assessed via PET. This finding is in line with several imaging studies on reward anticipation employing either fMRI or PET measures (Koepp et al., 1998; Knutson et al., 2000; Pappata et al., 2002; Wittmann et al., 2005) and provides direct support for the comparability of hemodynamic processes and dopaminergic neurotransmission during rewarded tasks.

One important limitation of the comparative approach employing fMRI and PET measures is the difference in temporal resolution. While fMRI provides a resolution of approximately two sec for an event-related design, PET allows only for a cumulative DA release within one scanning session. With regard to the fMRI experiment, we were able to clearly dissociate reward anticipation and outcome phase, while those remain conflated in the PET scan. Thus, it is likely that fMRI reflects the fast burst firing of DA neurons in response to a reward-predicting cue (Schultz, 1998), while changes in PET BP_{ND} might additionally depend on the tonic baseline firing of this neurons to cumulative reward. However, given the observed correlation between reward-related [^{11}C]raclopride BP_{ND} decrease in the left NAcc and the BOLD signal within SN/VTA during reward anticipation, we strongly hypothesize that the observed tracer displacement might be, at least to a considerable proportion, a result of midbrain burst firing to reward-predicting cues. The possibility remains, that changes in the tonic firing rate of SN/VTA neurons contributed quantitatively to the observed BP_{ND} reduction and that the correlation with the SN/VTA BOLD response was driven by the fact that only the proportion of tonically active SN/VTA neurons can burst-fire. It has been shown in monkeys and rodents, that the fMRI BOLD signal is related to local field potentials, which should reflect postsynaptic mechanisms as well as local neuronal activity (Logothetis, 2002; Knutson and Gibbs, 2007). The results of Exp 3 regarding SN/VTA

activations might thus result from both local neuronal firing and increased activations from other input structures.

The ventral striatum, in which a correlation between fMRI activation and DA release was also observed, might exert indirect excitatory influence on the midbrain by inhibiting GABAergic neurons of the ventral pallidum that tonically inhibit the dopaminergic midbrain neurons (Lisman and Grace, 2005). The NAcc itself receives excitatory input from the amygdala and hippocampus, structures that also showed a positive correlation between reward-related DA release and fMRI activation during reward anticipation (see Fig. 14). However, the short latency of the midbrain DA signal is indicative of a more direct efferent input to the dopaminergic midbrain, for example from the pedunculopontine nucleus of the brainstem (Kobayashi and Okada, 2007). While the amygdala has traditionally been implicated in aversive learning, human neuroimaging studies have further suggested that the amygdala might actually participate in the prediction of the reward values (Gottfried et al., 2003). It has been demonstrated that the amygdala responds to the magnitude of an expected reward (Marsh et al., 2007), and invasive recordings in monkeys have shown that dopaminergic neurons code reward values adaptively (Roesch and Olson, 2007). We tentatively suggest that the amygdala might be one of the structures that signal the expected reward value to the midbrain, thereby determining the magnitude of the phasic DA response.

As the relationship between activation of the metabotropic DA receptors and neurovascular coupling is only partly understood, the correlation of tracer displacement with the fMRI activation of the NAcc is more difficult to interpret. In Exp 3, the ventral striatal BOLD response to reward anticipation correlates positively with DA release in the same rewarded task. One explanation for this observation would be that the positive correlation between the observed [^{11}C]raclopride BP_{ND} reduction in PET and ventral striatal activation in fMRI results from the local DA release. It has been suggested that the BOLD signal reflects the postsynaptic effects of DA on the D1 rather than on D2 receptors in the striatum (Knutson and Gibbs, 2007). The effects of synaptic DA on neurovascular coupling are, however, not completely understood. Choi and colleagues suggested that DA-mediated increases of regional cerebral blood

volume in rodents might result from dopaminergic action at postsynaptic or vascular D1 type DA receptors (Choi et al., 2006). Alternative to the possibility of a direct local relationship between DA release and BOLD is an indirect relationship resulting from NAcc stimulation of the SN/VTA via ventral pallidum as described above.

7. General Discussion

7.1. Modulation of reward anticipation by stimulus novelty

7.1.1. The novelty exploration bonus

In experiments 1 and 2 we investigated how the novelty of reward-predicting stimuli influences the mesolimbic BOLD response during reward anticipation. Previously a mesolimbic novelty response during both implicit and explicit processing of novel stimuli (Schott et al., 2004; Bunzeck and Duzel, 2006) as well as during anticipation of novelty (Wittmann et al., 2007) has been reported. We therefore hypothesized that novelty of reward-predicting cues would lead to an enhanced reward anticipation response of the SN/VTA and the ventral striatum irrespective of task instructions. We, however, found that the predicted enhancing effect of novelty on mesolimbic reward prediction was strongly task-dependent and was observed only when novelty processing was implicit to the current task, that is, when assessment of reward-predictive properties required an explicit decision (Exp 2). When, in contrast, explicit novel/familiar judgments were required during cue presentation and the reward-predictive properties of the cue remained implicit, subjects showed a reduced tendency of the mesolimbic reward anticipation response for novel cues (Exp 1). The lack of robust anticipation in response to the cue was reflected in an enhanced response to positive outcome following novel cues within the ventral striatum in Exp1, and for positive outcome following familiar cues in Exp 2.

As the same stimulus material and almost the same paradigm were used in both experiments, the differences in mesolimbic reward response might be due to attentional modulations produced by different task instructions. One possible explanation for this modulation might be that explicit novelty detection requires considerable allocation of cognitive resources compared to the recognition of familiar items. This would be compatible with the observed activations in the visuo-spatial attention and selection regions, such as the lateral occipital cortex and the dACC and the significantly longer RTs for novel as compared to familiar cue pictures in Exp 1. The higher demands regarding resource allocation might arise from different decision strategies in both experiments. In

Exp 1, subjects had to perform a retrieval-based decision, which is likely to require an analysis of perceptual details of the cue pictures and therefore more cognitive resources have to be allocated. This task was especially difficult in case of novel cues, because subjects had to perform an initial visual search and did not have the possibility to use anchor details for orientation. In contrast, the decision in Exp 2 was mainly based on categorical classification between indoor and outdoor and thus easier to perform for all picture cues. The observed increased activity in the dACC during encoding of novel stimuli in Exp 1 relative to Exp 2 provides support for the hypothesis that subjects had to allocate more cognitive resources to process novel stimuli (see Fig. 9). Since the dACC has previously been associated with conflict processing, decision making, and risk evaluation (Barch et al., 2001; Landmann et al., 2007; Marsh et al., 2007), we suggest that the dACC might exert a control function over the ventral striatum in rewarded tasks which ultimately leads to an attenuation of the mesolimbic response. In Exp 1, the successful prediction of subsequent rewards was impaired for novel stimuli, although the implicit reward-predicting features (i.e. indoor versus outdoor scenes) had been well learned and could be successfully applied for the familiar cue pictures.

In a recent study that used a similar paradigm employing explicit reward prediction, an impaired shift of the mesolimbic response to the presentation of the reward-predicting cue was observed in healthy elderly and patients with Parkinson's disease (Schott et al., 2007). The impaired learning of the association between reward-predicting cue and rewarding outcome might reflect the reduced cognitive flexibility in these populations. Linking these findings to the results of Exp 1 and Exp 2, we suggest that performance of cognitively demanding tasks might attenuate the ability to retrieve previously learned stimulus-reward associations. One might argue that the salience of stimulus novelty itself leads to a shift of attentional resources away from the reward-predicting property of the item. However, if such a shift of attention was automatic, it should also occur in Exp 2 during explicit reward prediction, which was not the case. Here, mesolimbic reward prediction was actually enhanced for novel relative to familiar items.

This observation is in line with animal models reporting that rats prefer previously novelty-paired over familiar environments in the absences of natural reinforcers (e.g. (Bardo et al., 1996; Bevins and Besheer, 2005) and that novel stimuli could reduce the number of drug self-administrations (e.g. (Cain et al., 2004; Cain et al., 2006b). Furthermore, Li and colleagues observed an enhanced dopaminergic activity and increases in LTP by stimulus novelty in rats, emphasizing the role of DA in novelty encoding and memory formation (Li et al., 2003). It has been suggested that an innate tendency to explore novel events is an important property of foraging species (Panksepp, 1998; Knutson and Cooper, 2006) and there is recent evidence from human functional neuroimaging for increased activation of the dopaminergic midbrain during processing of novel stimuli (Schott et al., 2004; Bunzeck and Duzel, 2006; Wittmann et al., 2007). The findings of experiments 1 and 2 have shown that novelty can act as an exploration bonus for rewards (Kakade and Dayan, 2002) in a way that stimulus novelty enhances reward anticipation under conditions where attention is directed towards future rewards (see Fig. 7). Since the current paradigm used a rather indirect approach, the results might not be sufficient to provide a clear quantification of the exploration bonus on the basis of computational models. Nevertheless, our data is convincingly consistent with the proposition that novelty holds an exploration bonus promoting a continued exploration for rewards in novel environments rather than being a reward itself. Furthermore, these findings support the suggestion that novelty energizes behavior by providing mesencephalic DA and thus interacts with incentive-related tasks (Berridge, 2007; Niv et al., 2007; Robbins and Everitt, 2007). It remains to be determined whether the motivational effects of novelty demonstrated here are functionally related to incentive motivation of approach behavior. The results of the measure for behavioral performance in the current experiments, the number comparison task, provide evidence for a fastened response after reward-predicting but not after novel cues. Recent evidence from our group also indicates that novelty can enhance human learning of items presented in the context of novelty in the absence of changes in behavioral reaction times (Bunzeck and Duzel, 2006; Fenker et al., 2008).

The assumption of a novelty exploration bonus relates to natural exploratory behaviors which are difficult to simulate in an fMRI experiment. In our experimental design, we tried to approach this concept by signaling reward prediction through different types of natural environments, i.e. photographs of indoor and outdoor scenes. Although we cannot make a direct link with physical and mobile exploration, we believe that the visual exploration of images containing natural scenes provided a reasonable substitute.

With regard to the dissociation between stimulus novelty and contextual novelty, it should be noted, that earlier findings provided evidence for a rather disadvantageous role of stimulus novelty in attentional processing compared to contextual novelty (Ranganath and Rainer, 2003). It has been stated that stimulus novelty might be associated with a disadvantage because it takes more effort to encode absolute unknown items, while the encoding of familiar stimuli is facilitated and the reduction of neural activity allows for a more efficient processing of parallel ongoing tasks. In contrast, contextual novelty might be associated with an advantage for the oddball by raising attention thereby enhancing sensory processing and encoding success. Although we exclusively investigated stimulus novelty in our paradigm, the encoding of novel items was actual facilitated when subjects attended to the rewarding properties of the item and not to stimulus novelty (Exp 2). In contrast, the hypothesis that stimulus novelty might hold disadvantages is supported by the data of Exp 1 in which the emphasis lies on the actual encoding of novel items. Taken together, our data thus indicates that whether stimulus novelty is positive or negative in sense of allocation of resources is strongly dependent on the current task and the interaction with other stimulus properties such as reward-prediction that promote motivation.

7.1.2. Impact of reward processing on retrieval

Retrieval performance rates of the delayed memory test in experiments 1 and 2 confirm that long-term memory was more accurate for pictures environments that predicted rewards compared to neutral scenes (see Figures 4c and 6c). Since a 24 hours delay between encoding and retrieval was used, it appears that the impact of reward on encoding was long-lasting, compatible with earlier

data showing that reward enhances consolidation (Wittmann et al., 2005). However, we cannot exclude that reward also had an effect on encoding itself, which would have been apparent in memory tests after a short retention interval. With regard to the underlying brain activity, the reward-related memory improvement for scenes was accompanied by a reliable enhancement of hippocampal activity in response to reward-predicting cues in both experiments. This enhancement of hippocampal activation by reward-predicting stimuli replicates previous findings (Wittmann et al., 2005). In the current experiments, the reward-related modulation of hippocampal activity was more consistent than the modulation by stimulus novelty, which had been shown earlier. Therefore, this hippocampal activation by rewards might indicate that the hippocampus is activated by the motivational value of scenes and this activation is then associated with improved memory for the reward-predicting scenes (Lisman and Grace, 2005). This motivational account would be compatible with a recent observation that hippocampal activity can be elicited already by symbolic and highly familiarized cues that predict novelty (Wittmann et al., 2007), hence again linking its activity to a motivational and not only to a stimulus novelty account.

While the observation that anticipation of rewards enhances declarative long-term memory is well-established (Wittmann et al., 2005; Adcock et al., 2006), it has so far not been clear whether responses to actual rewards, which occur during the outcome phase when cue-reward associations had not been well established, would also modulate declarative long-term memory. Given that the work on reinforcement learning suggests that prediction-errors, in terms of computational models, are learning signals for cue-reward associations (Sutton, 1998), it is likely that responses to reward outcome might also modulate declarative long-term memory. To address this issue, we compared the BOLD responses during the outcome phase to the performance in the delayed memory test and observed a striking similarity between both patterns. Although the underlying interaction of the behavioral data was not statistically significant, the similarity of both patterns suggests that responses to reward outcome can modulate declarative memory for the preceding cue. If replicable, this would suggest an extension of reinforcement learning theories

with the possibility that responses to reward outcome of reward also serve as modulatory learning signals enhancing long-term declarative memories even when the retrieval of these memories is not task-dependent on associations with rewards.

7.2. Inter-individual differences

We found that inter-individual differences as assessed by the TCI-scales had a reliable effect on mesolimbic novelty and reward processing. While *RewD* is correlated with SN/VTA activation for novel stimuli that do predict reward, *NovS* is associated with elevated levels of novelty-related activation in the SN/VTA for novel stimuli in the absence of reward. Together, these findings provide evidence for a functional dissociation between behavioral valence of novelty and reward. For novelty-seekers, the motivational valence of novel stimuli does not depend on the explicit prediction of reward and for individuals scoring high in *RewD*, novel stimuli are not equivalent to stimuli that explicitly predict rewards. In addition, the negative relationship between *RewD* and the BOLD response to familiar reward-predicting cues within right hippocampus might reflect an altered hippocampal sensitivity for reward. Subjects that are highly dependent on rewards seem to need more reward-related input to reach a comparable hippocampal activation level.

The dissociation between novelty- and reward-related personality traits provides support for the theory that novelty acts as an exploration bonus for rewards rather than being a substitute for reward (Kakade and Dayan, 2002). However, the data show that representations of reward and novelty in the SN/VTA cannot be entirely independent. This is illustrated by the negative correlation between SN/VTA responses to novel stimuli that did not predict reward and the additional activation by reward-prediction. Physiologically, these two seemingly opposing findings could be reconciled through long-lasting adaptive changes in the connectivity of SN/VTA neurons. In individuals with high *ExpE*, a larger proportion of the population of DA neurons may be entrained into networks specialized in novelty processing, whereas in high reward-dependent subjects the pattern may be opposite. Hence, novelty and

reward, rather than competing for the same pool of dopaminergic neurons in the SN/VTA, may have variable sizes of pre-allocated populations of dopaminergic neurons in individuals with different personality traits.

Furthermore, novelty seeking seems to be linked to memory processing in interaction with reward, in a way that novelty-seekers need less reward to achieve comparable recollection performance. Although neither SN/VTA activity to novel neutral stimuli nor *ExpE* predicted individual recollection scores for novel neutral stimuli, both *ExpE* and SN/VTA activity determined how much individuals' recollection would benefit from reward-anticipation. Low levels lead to stronger enhancement by rewards than higher levels of SN/VTA activity (negative correlation between SN/VTA activity to novel neutral stimuli and the SN/VTA activity difference between novel neutral and novel reward-predicting stimuli r=-.41, p=.027) and the magnitude of SN/VTA activity enhancement by reward is correlated with the recollection benefit from reward (positive correlation between SN/VTA activity difference between novel neutral and novel reward-predicting stimuli the recollection difference between reward-predicting novel stimuli and novel-neutral stimuli r=.52, p=.004). This relationship between reward-related activation of SN/VTA and hippocampus-dependent memory strengthens previous observations (Wittmann et al., 2005) (Adcock et al., 2006) and extends the relationship to inter-individual differences.

Since *NovS* is linked to the source region of DA neurons in the midbrain and the relationship is not dependent on the rewarding properties of the stimulus but on stimulus novelty per se, this trait seems to be 'hard-wired'. One interesting question that arises from these findings concerns the direction of causality. Specifically, the individual novelty seeking trait might interact with a certain situation entailing novelty to lead to a certain neurobiological response, or state, with 'novelty-seekers' displaying stronger dopaminergic responses to novel situations in the absence of actual reward. Alternatively, these situational fluctuations in the DA-system could be causal for novelty seeking behavior and, relying on the motivating characteristics of DA, drive the subject to seek for novel situations (i.e. the recurring experiencing of the state is actually causal for

the trait). Unfortunately, the current results do not permit to clearly distinguish between the two notions.

Novelty seeking has been discussed as a predictor of drug use and other reinforcable risky behaviors (Howard et al., 1997). The currrent data do not support the proposition that individuals with high *NovS* are likely to experience greater reinforcing effects during novelty exposure (Wills et al., 1994; Zuckerman and Kuhlman, 2000) that is suggested to lead to their pursuit of exciting, but potentially risky situations. Rather, the findings are in line with the notion that novelty-seekers tend to show a generally upregulated novelty-induced exploratory behavior – even when novelty does not predict reward. Furthermore, the current results could be linked to research on attention-deficit/hyperactivity disorder (ADHD). It has been shown, that although ADHD is associated with higher novelty seeking scores compared to controls (Anckarsater et al., 2006), patients show a decreased striatal reward anticipation response (Strohle et al., 2008). These observations are compatible with the findings that novelty seeking is not necessarily based on actual reward-predicting stimulus properties.

7.3. fMRI meets PET

The data of the combined PET/fMRI experiment provide compelling evidence for a relationship between reward-related mesolimbic activations and the amount of DA release within ventral striatum during the same task. This finding confirms the interpretations of experiments 1 and 2 and is compatible with human pharmacological investigations that demonstrate a modulation of mesolimbic reward prediction-errors by DA-related drugs (Pessiglione et al., 2006).

The traditional view that links the dopaminergic midbrain response to the prediction-error concept has been recently challenged by the argument that the very early onset and short duration of the DA signal would only allow for a relatively crude sensory analysis by subcortical structures (Dommett et al., 2005; Redgrave et al., 2007). From this perspective, the phasic dopaminergic firing might rather be an unspecific response to salient sensory events that

coincides with a more elaborate neuronal processing in the striatum. However, this hypothesis is not incompatible with the observed positive correlation of DA release and ventral striatal activation, as even an unspecific dopaminergic signal might be able to enhance local glutamatergic neurotransmission. Furthermore, the observation that responses within hippocampus and amygdala were also correlated with DA release in the NAcc (see Fig. 14) cannot be sufficiently explained by an early, unspecific DA response. This finding is rather more compatible with the view that DA release is modulated by limbic afferences that might convey higher-level analysis of sensory input to the SN/VTA (Lisman and Grace, 2005). In Exp 3, processing of reward required a high level of conceptual analysis of stimulus information and because each stimulus was novel, this type of analysis could not have been transferred to low-level visual areas by repetition such as the superior colliculus, a midbrain structure that has been implicated in providing direct low-level visual input to the SN/VTA (Redgrave et al., 2007). Hence, the data of Exp 3 shows that during the presentation of natural reward-cues, activations within the hippocampal-VTA loop (Lisman and Grace, 2005) are correlated with striatal DA release. This finding is in line with the assumption that limbic input transfers reward-related information to the SN/VTA.

7.4. Implications and outlook

The findings of the work presented in this thesis contribute to a better understanding of the interaction between reward and novelty processing and the underlying dopaminergic neurotransmission with regard to approach behavior and motivation. The implications of this line of research are manifold. I would like to mention just two, namely education and addiction.

The earlier suggestion that learning and memory formation could be positively influenced by reward-prediction (Wittmann et al., 2005; Adcock et al., 2006) could be extended in a way that novelty promotes continued exploration in reward-predicting situations and thus might further enhance memory consolidation. Based on the assumption that stimulus novelty can serve as an exploration bonus, it would be of interest to further investigate under which

conditions this advantageous relationship appears. Since a stimulus could hold other additional properties aside from being novel or familiar, i.e. emotional salience, the interaction of novelty and reward regarding mesolimbic activity should also be related to the recently reported influence of emotional salience on reward anticipation (Wittmann et al., 2008) in future research.

Although the PET/fMRI study is restricted to the reward construct, the results of Exp 3 also bear on the interpretation of Exp 1 and 2. Since we demonstrated that novelty can act as an exploration bonus in the context of reward (Exp 2), it is likely that the novelty-dependent enhancement of mesolimbic reward anticipation is also reflected in increased striatal DA release. Thus, the direct link of novelty encoding to dopaminergic neurotransmission might be investigated in future research employing combined reward and novelty processing paradigms via PET. Future research could be directed towards the influence of dopaminergic neuromodulation on other cognitive functions like working memory (O'Reilly and Frank, 2006) and hippocampus-dependent memory consolidation (Wittmann et al., 2005; Adcock et al., 2006). The comparative PET/fMRI approach could be also useful to systematically investigate alterations of the relationship between DA release and event-related hemodynamic brain activity patterns in DA-related disorders (e.g. Parkinson's disease and schizophrenia) and thus help to further elucidate how pathological changes in the DA system contribute to cognitive and behavioral dysfunction.

The influence of novelty seeking and reward dependence on the mesolimbic activity in response to reward-predicting cues confirms the link between dopaminergic neurotransmission and specific personality traits. Since novelty seeking enhances general exploratory behavior, it is associated with a higher probability to detect and receive rewards. Although both dimensions are independent in normal distributed populations, high scores in both dimensions might be predictive of a high risk for substance abuse (Howard et al., 1997); (Bardo et al., 1996). The proposition that subjects with high *NovS* are likely to experience greater reinforcing effects of novel stimuli based on the assumption that novelty is intrinsically rewarding and thus may lead to pursuit of exciting, but often risky situations (Wills et al., 1994); (Zuckerman and Kuhlman, 2000) is

not supported by the data presented here. The current findings rather stress the upregulation of novelty-induced exploratory behavior even in situations where novelty does not explicitly predict reward. From a psychological point of view, a combination of high scores in both traits might lead to frequent initial approach to novel situations, including drug use, and subsequently result in an enhanced adherence to those situations that turned out to be actual rewarding. Thus, it might be worthwhile to bear the inter-individual differences in mind while developing preventive and medical solutions regarding addiction.

8. References

Abler B, Greenhouse I, Ongur D, Walter H, Heckers S (2007) Abnormal Reward System Activation in Mania. Neuropsychopharmacology.

Adcock RA, Thangavel A, Whitfield-Gabrieli S, Knutson B, Gabrieli JD (2006) Reward-motivated learning: mesolimbic activation precedes memory formation. Neuron 50:507-517.

Ahsan RL, Allom R, Gousias IS, Habib H, Turkheimer FE, Free S, Lemieux L, Myers R, Duncan JS, Brooks DJ, Koepp MJ, Hammers A (2007) Volumes, spatial extents and a probabilistic atlas of the human basal ganglia and thalamus. Neuroimage 38:261-270.

Anckarsater H, Stahlberg O, Larson T, Hakansson C, Jutblad SB, Niklasson L, Nyden A, Wentz E, Westergren S, Cloninger CR, Gillberg C, Rastam M (2006) The impact of ADHD and autism spectrum disorders on temperament, character, and personality development. Am J Psychiatry 163:1239-1244.

Ashburner J, Friston KJ (1999) Nonlinear spatial normalization using basis functions. Hum Brain Mapp 7:254-266.

Badgaiyan RD, Schacter DL, Alpert NM (1999) Auditory priming within and across modalities: evidence from positron emission tomography. J Cogn Neurosci 11:337-348.

Barch DM, Braver TS, Akbudak E, Conturo T, Ollinger J, Snyder A (2001) Anterior Cingulate Cortex and Response Conflict: Effects of Response Modality and Processing Domain. Cereb Cortex 11:837-848.

Bardo MT, Bevins RA (2000) Conditioned place preference: what does it add to our preclinical understanding of drug reward? Psychopharmacology (Berl) 153:31-43.

Bardo MT, Donohew RL, Harrington NG (1996) Psychobiology of novelty seeking and drug seeking behavior. Behav Brain Res 77:23-43.

Baxter MG, Murray EA (2002) The amygdala and reward. Nat Rev Neurosci 3:563-573.

Benjamin J, Osher Y, Kotler M, Gritsenko I, Nemanov L, Belmaker RH, Ebstein RP (2000) Association between tridimensional personality questionnaire (TPQ) traits and three functional polymorphisms: dopamine receptor D4 (DRD4), serotonin transporter promoter region (5-HTTLPR) and catechol O-methyltransferase (COMT). Mol Psychiatry 5:96-100.

Berns GS, McClure SM, Pagnoni G, Montague PR (2001) Predictability modulates human brain response to reward. J Neurosci 21:2793-2798.

Berridge KC (2007) The debate over dopamine's role in reward: the case for incentive salience. Psychopharmacology (Berl) 191:391-431.

Bevins RA, Besheer J (2005) Novelty reward as a measure of anhedonia. Neurosci Biobehav Rev 29:707-714.

Bevins RA, Besheer J, Palmatier MI, Jensen HC, Pickett KS, Eurek S (2002) Novel-object place conditioning: behavioral and dopaminergic processes in expression of novelty reward. Behav Brain Res 129:41-50.

Björklund A, Dunnett SB (2007) Dopamine neuron systems in the brain: an update. Trends in Neurosciences 30:194-202.

Blum K, Braverman ER, Holder JM, Lubar JF, Monastra VJ, Miller D, Lubar JO, Chen TJ, Comings DE (2000) Reward deficiency syndrome: a biogenetic

model for the diagnosis and treatment of impulsive, addictive, and compulsive behaviors. J Psychoactive Drugs 32 Suppl:i-iv, 1-112.

Bowirrat A, Oscar-Berman M (2005) Relationship between dopaminergic neurotransmission, alcoholism, and Reward Deficiency syndrome. Am J Med Genet B Neuropsychiatr Genet 132:29-37.

Braver TS, Barch DM, Cohen JD (1999) Cognition and control in schizophrenia: a computational model of dopamine and prefrontal function. Biological Psychiatry 46:312-328.

Breiter HC, Aharon I, Kahneman D, Dale A, Shizgal P (2001) Functional imaging of neural responses to expectancy and experience of monetary gains and losses. Neuron 30:619-639.

Brett M, Anton J-L, Valabregue R, Poline J-P (2002) Region of interest analysis using an SPM toolbox [abstract]. In: 8th International Conference on Functional Mapping of the Human Brain. Sendai, Japan.

Brown MW, Xiang JZ (1998) Recognition memory: neuronal substrates of the judgement of prior occurrence. Progress in Neurobiology 55:149-189.

Bunzeck N, Duzel E (2006) Absolute coding of stimulus novelty in the human substantia nigra/VTA. Neuron 51:369-379.

Bunzeck N, Schutze H, Stallforth S, Kaufmann J, Duzel S, Heinze H-J, Duzel E (2007) Mesolimbic Novelty Processing in Older Adults. Cereb Cortex:bhm020.

Bush G, Luu P, Posner MI (2000) Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn Sci 4:215-222.

Cain ME, Smith CM, Bardo MT (2004) The effect of novelty on amphetamine self-administration in rats classified as high and low responders. Psychopharmacology (Berl) 176:129-138.

Cain ME, Saucier DA, Bardo MT (2005) Novelty seeking and drug use: contribution of an animal model. Exp Clin Psychopharmacol 13:367-375.

Cain ME, Green TA, Bardo MT (2006a) Environmental enrichment decreases responding for visual novelty. Behav Processes 73:360-366.

Cain ME, Dotson WF, Bardo MT (2006b) Individual differences in the effect of novel environmental stimuli prior to amphetamine self-administration in rats (Rattus norvegicus). Exp Clin Psychopharmacol 14:389-401.

Cardinal RN, Parkinson JA, Hall J, Everitt BJ (2002) Emotion and motivation: the role of the amygdala, ventral striatum, and prefrontal cortex. Neurosci Biobehav Rev 26:321-352.

Carver CS, White TL (1994) Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: The BIS/BAS Scales. Journal of Personality and Social Psychology 67:319-333.

Cheer JF, Aragona BJ, Heien ML, Seipel AT, Carelli RM, Wightman RM (2007) Coordinated accumbal dopamine release and neural activity drive goal-directed behavior. Neuron 54:237-244.

Choi JK, Chen YI, Hamel E, Jenkins BG (2006) Brain hemodynamic changes mediated by dopamine receptors: Role of the cerebral microvasculature in dopamine-mediated neurovascular coupling. Neuroimage 30:700-712.

Cloninger CR (1986) A unified biosocial theory of personality and its role in the development of anxiety states. Psychiatr Dev 4:167-226.

Cloninger CR (1987) A systematic method for clinical description and classification of personality variants. A proposal. Arch Gen Psychiatry 44:573-588.

Cloninger CR (1988) A unified biosocial theory of personality and its role in the development of anxiety states: a reply to commentaries. Psychiatr Dev 6:83-120.

Cloninger CR (1991) The Temperament and Character Inventory (TCI): a guide to its development and use. St Louis, Missouri: Washington University.

Cloninger CR (1994) The Temperament and Character Inventory (TCI): a guide to its development and use. St Louis, Missouri: Washington University.

Cloninger CR, Przybeck TR, Svrakic DM (1991) The Tridimensional Personality Questionnaire: U.S. normative data. Psychol Rep 69:1047-1057.

Cloninger CR, Bayon C, Svrakic DM (1998) Measurement of temperament and character in mood disorders: a model of fundamental states as personality types. J Affect Disord 51:21-32.

Cohen MX (2007) Individual differences and the neural representations of reward expectation and reward prediction error. Soc Cogn Affect Neurosci 2:20-30.

Comings DE, Blum K (2000) Reward deficiency syndrome: genetic aspects of behavioral disorders. Prog Brain Res 126:325-341.

Cooper JC, Knutson B (2008) Valence and salience contribute to nucleus accumbens activation. NeuroImage 39:538-547.

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

Courchesne E, Hillyard SA, Galambos R (1975) Stimulus novelty, task relevance and the visual evoked potential in man. Electroencephalogr Clin Neurophysiol 39:131-143.

D'Ardenne K, McClure SM, Nystrom LE, Cohen JD (2008) BOLD responses reflecting dopaminergic signals in the human ventral tegmental area. Science 319:1264-1267.

Dayan P, Sejnowski TJ (1996) Exploration bonuses and dual control. Machine Learning 25:5-22.

de Frias CM, Annerbrink K, Westberg L, Eriksson E, Adolfsson R, Nilsson LG (2004) COMT gene polymorphism is associated with declarative memory in adulthood and old age. Behav Genet 34:533-539.

Delgado MR (2007) Reward-Related Responses in the Human Striatum. Ann NY Acad Sci 1104:70-88.

Delgado MR, Miller MM, Inati S, Phelps EA (2005) An fMRI study of reward-related probability learning. Neuroimage 24:862-873.

Delgado MR, Nystrom LE, Fissell C, Noll DC, Fiez JA (2000) Tracking the hemodynamic responses to reward and punishment in the striatum. J Neurophysiol 84:3072-3077.

Desimone R (1996) Neural mechanisms for visual memory and their role in attention. Proc Natl Acad Sci U S A 93:13494-13499.

Dommett E, Coizet V, Blaha CD, Martindale J, Lefebvre V, Walton N, Mayhew JE, Overton PG, Redgrave P (2005) How visual stimuli activate dopaminergic neurons at short latency. Science 307:1476-1479.

Downar J, Crawley AP, Mikulis DJ, Davis KD (2000) A multimodal cortical network for the detection of changes in the sensory environment. Nat Neurosci 3:277-283.

Downar J, Crawley AP, Mikulis DJ, Davis KD (2002) A Cortical Network Sensitive to Stimulus Salience in a Neutral Behavioral Context Across Multiple Sensory Modalities. J Neurophysiol 87:615-620.

Duzel E, Habib R, Guderian S, Heinze HJ (2004) Four types of novelty-familiarity responses in associative recognition memory of humans. Eur J Neurosci 19:1408-1416.

Duzel E, Habib R, Rotte M, Guderian S, Tulving E, Heinze HJ (2003) Human hippocampal and parahippocampal activity during visual associative recognition memory for spatial and nonspatial stimulus configurations. J Neurosci 23:9439-9444.

Eichenbaum H (2000) A cortical-hippocampal system for declarative memory. Nat Rev Neurosci 1:41-50.

Eichenbaum H, Yonelinas AP, Ranganath C (2007) The Medial Temporal Lobe and Recognition Memory. Annual Review of Neuroscience 30:123-152.

Ekelund J, Lichtermann D, Järvelin M-R, Peltonen L (1999) Association Between Novelty Seeking and the Type 4 Dopamine Receptor Gene in a Large Finnish Cohort Sample. Am J Psychiatry 156:1453-1455.

Elliott R, Newman JL, Longe OA, William Deakin JF (2004) Instrumental responding for rewards is associated with enhanced neuronal response in subcortical reward systems. Neuroimage 21:984-990.

Everitt BJ, Robbins TW (2005) Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. Nat Neurosci 8:1481-1489.

Fehr C, Yakushev I, Hohmann N, Buchholz HG, Landvogt C, Deckers H, Eberhardt A, Klager M, Smolka MN, Scheurich A, Dielentheis T, Schmidt LG, Rosch F, Bartenstein P, Grunder G, Schreckenberger M (2008) Association of Low Striatal Dopamine D2 Receptor Availability With Nicotine Dependence Similar to That Seen With Other Drugs of Abuse. Am J Psychiatry.

Fenker DB, Frey JU, Schuetze H, Heipertz D, Heinze HJ, Duzel E (2008) Novel Scenes Improve Recollection and Recall of Words. J Cogn Neurosci.

Floresco SB, Todd CL, Grace AA (2001) Glutamatergic afferents from the hippocampus to the nucleus accumbens regulate activity of ventral tegmental area dopamine neurons. J Neurosci 21:4915-4922.

Floresco SB, West AR, Ash B, Moore H, Grace AA (2003) Afferent modulation of dopamine neuron firing differentially regulates tonic and phasic dopamine transmission. Nat Neurosci 6:968-973.

Frey U, Matthies H, Reymann KG, Matthies H (1991) The effect of dopaminergic D1 receptor blockade during tetanization on the expression of long-term potentiation in the rat CA1 region in vitro. Neurosci Lett 129:111-114.

Fried I, Wilson CL, Morrow JW, Cameron KA, Behnke ED, Ackerson LC, Maidment NT (2001) Increased dopamine release in the human amygdala during performance of cognitive tasks. Nat Neurosci 4:201-206.

Friedman D, Cycowicz YM, Gaeta H (2001) The novelty P3: an event-related brain potential (ERP) sign of the brain's evaluation of novelty. Neurosci Biobehav Rev 25:355-373.

Friston KJ, Josephs O, Rees G, Turner R (1998) Nonlinear event-related responses in fMRI. Magn Reson Med 39:41-52.

Gasbarri A, Sulli A, Packard MG (1997) The dopaminergic mesencephalic projections to the hippocampal formation in the rat. Prog Neuropsychopharmacol Biol Psychiatry 21:1-22.

Gerdjikov TV, Beninger RJ (2006) Place preference induced by nucleus accumbens amphetamine is impaired by local blockade of Group II metabotropic glutamate receptors in rats. BMC Neurosci 7:43.

Glautier S, Bankart J, Rigney U, Willner P (1998) Multiple variable interval schedule behaviour in humans: effects of ethanol, mood, and reinforcer size on responding maintained by monetary reinforcement. Behav Pharmacol 9:619-630.

Glimcher PW, Rustichini A (2004) Neuroeconomics: the consilience of brain and decision. Science 306:447-452.

Golimbet VE, Alfimova MV, Gritsenko IK, Ebshtein RP (2006) [Dopamine system genes and personality traits of extraversion and novelty seeking]. Zh Vyssh Nerv Deiat Im I P Pavlova 56:457-463.

Goto Y, Grace AA (2005) Dopaminergic modulation of limbic and cortical drive of nucleus accumbens in goal-directed behavior. Nat Neurosci 8:805-812.

Gottfried JA, O'Doherty J, Dolan RJ (2003) Encoding predictive reward value in human amygdala and orbitofrontal cortex. Science 301:1104-1107.

Gray JA (1970) The psychophysiological basis of introversion-extraversion. Behav Res Ther 8:249-266.

Gray JA (1991) The Neuropsychology of Temperament. In: Explorations in temperament: International perspectives on theory and measurement. Perspectives on individual differences (Strelau J, Angleitner A, eds), pp 105–128. New York: Plenum Press.

Groenewegen HJ, Wright CI, Beijer AV, Voorn P (1999) Convergence and segregation of ventral striatal inputs and outputs. Ann N Y Acad Sci 877:49-63.

Gruber T, Malinowski P, Muller MM (2004) Modulation of oscillatory brain activity and evoked potentials in a repetition priming task in the human EEG. Eur J Neurosci 19:1073-1082.

Grunwald T, Beck H, Lehnertz K, Blumcke I, Pezer N, Kurthen M, Fernandez G, Van Roost D, Heinze HJ, Kutas M, Elger CE (1999) Evidence relating human verbal memory to hippocampal N-methyl-D-aspartate receptors. Proc Natl Acad Sci U S A 96:12085-12089.

Gurden H, Tassin JP, Jay TM (1999) Integrity of the mesocortical dopaminergic system is necessary for complete expression of in vivo hippocampal-prefrontal cortex long-term potentiation. Neuroscience 94:1019-1027.

Gurden H, Takita M, Jay TM (2000) Essential Role of D1 But Not D2 Receptors in the NMDA Receptor-Dependent Long-Term Potentiation at Hippocampal-Prefrontal Cortex Synapses In Vivo. J Neurosci 20:106RC.

Habib R, McIntosh AR, Wheeler MA, Tulving E (2003) Memory encoding and hippocampally-based novelty/familiarity discrimination networks. Neuropsychologia 41:271-279.

Hakamata Y, Iwase M, Iwata H, Kobayashi T, Tamaki T, Nishio M, Kawahara K, Matsuda H, Ozaki N, Honjo S, Inada T (2006) Regional brain cerebral glucose metabolism and temperament: a positron emission tomography study. Neurosci Lett 396:33-37.

Hansenne M, Pinto E, Pitchot W, Reggers J, Scantamburlo G, Moor M, Ansseau M (2002) Further evidence on the relationship between dopamine and novelty seeking: a neuroendocrine study. Personality and Individual Differences 33:967-977.

Hariri AR, Mattay VS, Tessitore A, Fera F, Weinberger DR (2003) Neocortical modulation of the amygdala response to fearful stimuli. Biol Psychiatry 53:494-501.

Heinz A, Siessmeier T, Wrase J, Buchholz HG, Grunder G, Kumakura Y, Cumming P, Schreckenberger M, Smolka MN, Rosch F, Mann K, Bartenstein P (2005) Correlation of Alcohol Craving With Striatal Dopamine Synthesis Capacity and D2/3 Receptor Availability: A Combined [18F]DOPA and [18F]DMFP PET Study in Detoxified Alcoholic Patients. Am J Psychiatry 162:1515-1520.

Heinz A, Siessmeier T, Wrase J, Hermann D, Klein S, Grusser-Sinopoli SM, Flor H, Braus DF, Buchholz HG, Grunder G, Schreckenberger M, Smolka MN, Rosch F, Mann K, Bartenstein P (2004) Correlation Between Dopamine D2 Receptors in the Ventral Striatum and Central Processing of Alcohol Cues and Craving. Am J Psychiatry 161:1783-1789.

Helmus TC, Downey KK, Arfken CL, Henderson MJ, Schuster CR (2001) Novelty seeking as a predictor of treatment retention for heroin dependent cocaine users. Drug Alcohol Depend 61:287-295.

Henson RNA, Rugg MD (2003) Neural response suppression, haemodynamic repetition effects, and behavioural priming. Neuropsychologia 41:263-270.

Higgins ST (1997) The influence of alternative reinforcers on cocaine use and abuse: a brief review. Pharmacol Biochem Behav 57:419-427.

Hjelmstad GO (2004) Dopamine excites nucleus accumbens neurons through the differential modulation of glutamate and GABA release. J Neurosci 24:8621-8628.

Holland PC, Gallagher M (2004) Amygdala-frontal interactions and reward expectancy. Curr Opin Neurobiol 14:148-155.

Hommer DW, Knutson B, Fong GW, Bennett S, Adams CM, Varnera JL (2003) Amygdalar recruitment during anticipation of monetary rewards: an event-related fMRI study. Ann N Y Acad Sci 985:476-478.

Horvitz JC (2000) Mesolimbocortical and nigrostriatal dopamine responses to salient non-reward events. Neuroscience 96:651-656.

Howard MO, Kivlahan D, Walker RD (1997) Cloninger's tridimensional theory of personality and psychopathology: applications to substance use disorders. J Stud Alcohol 58:48-66.

Huettel SA, Mack PB, McCarthy G (2002) Perceiving patterns in random series: dynamic processing of sequence in prefrontal cortex. Nat Neurosci 5:485-490.

Hunt RR (1995) The Subtlety of Distinctiveness - What Vonrestorff Really Did. Psychonomic Bulletin & Review 2:105-112.

Ihalainen JA, Riekkinen P, Jr., Feenstra MG (1999) Comparison of dopamine and noradrenaline release in mouse prefrontal cortex, striatum and hippocampus using microdialysis. Neurosci Lett 277:71-74.

Ikemoto S (2007) Dopamine reward circuitry: two projection systems from the ventral midbrain to the nucleus accumbens-olfactory tubercle complex. Brain Res Rev 56:27-78.

Ikemoto S, Panksepp J (1999) The role of nucleus accumbens dopamine in motivated behavior: a unifying interpretation with special reference to reward-seeking. Brain Res Rev 31:6-41.

Innis RB, Cunningham VJ, Delforge J, Fujita M, Gjedde A, Gunn RN, Holden J, Houle S, Huang SC, Ichise M, Iida H, Ito H, Kimura Y, Koeppe RA, Knudsen GM, Knuuti J, Lammertsma AA, Laruelle M, Logan J, Maguire RP, Mintun MA, Morris ED, Parsey R, Price JC, Slifstein M, Sossi V, Suhara T, Votaw JR, Wong DF, Carson RE (2007) Consensus nomenclature for in vivo imaging of reversibly binding radioligands. J Cereb Blood Flow Metab 27:1533-1539.

Jenkins TA, Amin E, Pearce JM, Brown MW, Aggleton JP (2004) Novel spatial arrangements of familiar visual stimuli promote activity in the rat hippocampal formation but not the parahippocampal cortices: a c-fos expression study. Neuroscience 124:43-52.

Jessen F, Manka C, Scheef L, Granath DO, Schild HH, Heun R (2002) Novelty detection and repetition suppression in a passive picture viewing task: a possible approach for the evaluation of neuropsychiatric disorders. Hum Brain Mapp 17:230-236.

Jessen F, Scheef L, Germeshausen L, Tawo Y, Kockler M, Kuhn K-U, Maier W, Schild HH, Heun R (2003) Reduced Hippocampal Activation During Encoding and Recognition of Words in Schizophrenia Patients. Am J Psychiatry 160:1305-1312.

Johnston WA, Hawley KJ, Farnham JM (1993) Novel Popout: Empirical Boundaries and Tentative Theory. Journal of Experimental Psychology: Human Perception and Performance 19:140-153.

Johnston WA, Hawley KJ, Plewe SH, Elliott JM, DeWitt MJ (1990) Attention capture by novel stimuli. J Exp Psychol Gen 119:397-411.

Josephs O, Henson RN (1999) Event-related functional magnetic resonance imaging: modelling, inference and optimization. Philos Trans R Soc Lond B Biol Sci 354:1215-1228.

Kakade S, Dayan P (2002) Dopamine: generalization and bonuses. Neural Netw 15:549-559.

Kenny PJ, Chen SA, Kitamura O, Markou A, Koob GF (2006) Conditioned withdrawal drives heroin consumption and decreases reward sensitivity. J Neurosci 26:5894-5900.

Kilpatrick MR, Rooney MB, Michael DJ, Wightman RM (2000) Extracellular dopamine dynamics in rat caudate-putamen during experimenter-delivered and intracranial self-stimulation. Neuroscience 96:697-706.

Kirchhoff BA, Wagner AD, Maril A, Stern CE (2000) Prefrontal-temporal circuitry for episodic encoding and subsequent memory. J Neurosci 20:6173-6180.

Kirino E, Belger A, Goldman-Rakic P, McCarthy G (2000) Prefrontal Activation Evoked by Infrequent Target and Novel Stimuli in a Visual Target Detection Task: An Event-Related Functional Magnetic Resonance Imaging Study. J Neurosci 20:6612-6618.

Kirsch P, Reuter M, Mier D, Lonsdorf T, Stark R, Gallhofer B, Vaitl D, Hennig J (2006) Imaging gene-substance interactions: the effect of the DRD2 TaqIA polymorphism and the dopamine agonist bromocriptine on the brain activation during the anticipation of reward. Neurosci Lett 405:196-201.

Kirsch P, Schienle A, Stark R, Sammer G, Blecker C, Walter B, Ott U, Burkart J, Vaitl D (2003) Anticipation of reward in a nonaversive differential

conditioning paradigm and the brain reward system: an event-related fMRI study. Neuroimage 20:1086-1095.

Kishiyama MM, Yonelinas AP, Lazzara MM (2004) The von Restorff effect in amnesia: the contribution of the hippocampal system to novelty-related memory enhancements. J Cogn Neurosci 16:15-23.

Klebaur JE, Phillips SB, Kelly TH, Bardo MT (2001b) Exposure to novel environmental stimuli decreases amphetamine self-administration in rats. Exp Clin Psychopharmacol 9:372-379.

Klega A, Buchholz H-G, Mueller C, Scheurich A, Schirrmacher R, Bartenstein P, Schreckenberger M (2007) Central opioidergic correlates of personality traits in healthy subjects. J NUCL MED MEETING ABSTRACTS 48:109P-b-.

Kliethermes CL, Crabbe JC (2006) Genetic independence of mouse measures of some aspects of novelty seeking. Proc Natl Acad Sci U S A 103:5018-5023.

Knecht S, Breitenstein C, Bushuven S, Wailke S, Kamping S, Floel A, Zwitserlood P, Ringelstein EB (2004) Levodopa: faster and better word learning in normal humans. Ann Neurol 56:20-26.

Knight RT, Nakada T (1998) Cortico-limbic circuits and novelty: a review of EEG and blood flow data. Rev Neurosci 9:57-70.

Knutson B, Cooper JC (2005) Functional magnetic resonance imaging of reward prediction. Curr Opin Neurol 18:411-417.

Knutson B, Cooper JC (2006) The lure of the unknown. Neuron 51:280-282.

Knutson B, Gibbs SE (2007) Linking nucleus accumbens dopamine and blood oxygenation. Psychopharmacology (Berl) 191:813-822.

Knutson B, Westdorp A, Kaiser E, Hommer D (2000) FMRI Visualization of Brain Activity during a Monetary Incentive Delay Task. NeuroImage 12:20-27.

Knutson B, Adams CM, Fong GW, Hommer D (2001a) Anticipation of increasing monetary reward selectively recruits nucleus accumbens. J Neurosci 21:RC159.

Knutson B, Fong GW, Adams CM, Varner JL, Hommer D (2001b) Dissociation of reward anticipation and outcome with event-related fMRI. Neuroreport 12:3683-3687.

Knutson B, Fong GW, Bennett SM, Adams CM, Hommer D (2003) A region of mesial prefrontal cortex tracks monetarily rewarding outcomes: characterization with rapid event-related fMRI. Neuroimage 18:263-272.

Knutson B, Taylor J, Kaufman M, Peterson R, Glover G (2005) Distributed neural representation of expected value. J Neurosci 25:4806-4812.

Kobayashi Y, Okada K-I (2007) Reward Prediction Error Computation in the Pedunculopontine Tegmental Nucleus Neurons. Ann NY Acad Sci 1104:310-323.

Koepp MJ, Gunn RN, Lawrence AD, Cunningham VJ, Dagher A, Jones T, Brooks DJ, Bench CJ, Grasby PM (1998) Evidence for striatal dopamine release during a video game. Nature 393:266-268.

Kohler S, Danckert S, Gati JS, Menon RS (2005) Novelty responses to relational and non-relational information in the hippocampus and the parahippocampal region: a comparison based on event-related fMRI. Hippocampus 15:763-774.

Kormi-Nouri R, Nilsson L-G, Ohta N (2005) The novelty effect: Support for the Novelty-Encoding Hypothesis. Scandinavian Journal of Psychology 46:133-143.

Kringelbach ML (2005) The human orbitofrontal cortex: linking reward to hedonic experience. Nat Rev Neurosci 6:691-702.

Kruzich PJ, Grandy DK (2004) Dopamine D2 receptors mediate two-odor discrimination and reversal learning in C57BL/6 mice. BMC Neurosci 5:12.

Kuo M-F, Paulus W, Nitsche MA (2007) Boosting Focally-Induced Brain Plasticity by Dopamine. Cereb Cortex:bhm098.

Lammertsma AA, Hume SP (1996) Simplified reference tissue model for PET receptor studies. Neuroimage 4:153-158.

Landmann C, Dehaene S, Pappata S, Jobert A, Bottlaender M, Roumenov D, Le Bihan D (2007) Dynamics of prefrontal and cingulate activity during a reward-based logical deduction task. Cereb Cortex 17:749-759.

Lee SH, Ham BJ, Cho YH, Lee SM, Shim SH (2007) Association study of dopamine receptor D2 TaqI A polymorphism and reward-related personality traits in healthy Korean young females. Neuropsychobiology 56:146-151.

Legault M, Wise RA (2001) Novelty-evoked elevations of nucleus accumbens dopamine: dependence on impulse flow from the ventral subiculum and glutamatergic neurotransmission in the ventral tegmental area. Eur J Neurosci 13:819-828.

Leyton M, Boileau I, Benkelfat C, Diksic M, Baker G, Dagher A (2002) Amphetamine-induced increases in extracellular dopamine, drug wanting, and novelty seeking: a PET/[11C]raclopride study in healthy men. Neuropsychopharmacology 27:1027-1035.

Li S, Cullen WK, Anwyl R, Rowan MJ (2003) Dopamine-dependent facilitation of LTP induction in hippocampal CA1 by exposure to spatial novelty. Nat Neurosci 6:526-531.

Lisman JE, Fallon JR (1999) What maintains memories? Science 283:339-340.

Lisman JE, Grace AA (2005) The Hippocampal-VTA Loop: Controlling the Entry of Information into Long-Term Memory. Neuron 46:703-713.

Ljungberg T, Apicella P, Schultz W (1992) Responses of monkey dopamine neurons during learning of behavioral reactions. J Neurophysiol 67:145-163.

Lodge DJ, Grace AA (2005) The Hippocampus Modulates Dopamine Neuron Responsivity by Regulating the Intensity of Phasic Neuron Activation. Neuropsychopharmacology 31:1356-1361.

Logan J, Fowler JS, Volkow ND, Wang GJ, Ding YS, Alexoff DL (1996) Distribution volume ratios without blood sampling from graphical analysis of PET data. J Cereb Blood Flow Metab 16:834-840.

Logothetis NK (2002) The neural basis of the blood-oxygen-level-dependent functional magnetic resonance imaging signal. Philos Trans R Soc Lond B Biol Sci 357:1003-1037.

Marsh AA, Blair KS, Vythilingam M, Busis S, Blair RJR (2007) Response options and expectations of reward in decision-making: The differential roles of dorsal and rostral anterior cingulate cortex. NeuroImage 35:979-988.

Martinez D, Slifstein M, Broft A, Mawlawi O, Hwang D-R, Huang Y, Cooper T, Kegeles L, Zarahn E, Abi-Dargham A, Haber SN, Laruelle M (2003) Imaging Human Mesolimbic Dopamine Transmission With Positron Emission Tomography. Part II[colon] Amphetamine-Induced Dopamine Release in the Functional Subdivisions of the Striatum. J Cereb Blood Flow Metab 23:285-300.

Matthews PM (2001) An introduction to functional magnetic resonance imaging of the brain. In: Functional magnetic resonance imaging: An introduction to methods (Jezzard P, Matthews PM, Smith SM, eds), pp 3-35. Oxford: University Press.

Mawlawi O, Martinez D, Slifstein M, Broft A, Chatterjee R, Hwang D-R, Huang Y, Simpson N, Ngo K, Van Heertum R, Laruelle M (2001) Imaging Human Mesolimbic Dopamine Transmission With Positron Emission Tomography[colon] I. Accuracy and Precision of D2 Receptor Parameter Measurements in Ventral Striatum. J Cereb Blood Flow Metab 21:1034-1057.

McClure SM, Daw ND, Read Montague P (2003) A computational substrate for incentive salience. Trends in Neurosciences 26:423-428.

McClure SM, York MK, Montague PR (2004) The neural substrates of reward processing in humans: the modern role of FMRI. Neuroscientist 10:260-268.

McClure SM, Ericson KM, Laibson DI, Loewenstein G, Cohen JD (2007) Time Discounting for Primary Rewards. J Neurosci 27:5796-5804.

Meltzer JA, Constable RT (2005) Activation of human hippocampal formation reflects success in both encoding and cued recall of paired associates. Neuroimage 24:384-397.

Menon V, White CD, Eliez S, Glover GH, Reiss AL (2000) Analysis of a distributed neural system involved in spatial information, novelty, and memory processing. Hum Brain Mapp 11:117-129.

Miller EK, Gochin PM, Gross CG (1991) Habituation-like decrease in the responses of neurons in inferior temporal cortex of the macaque. Vis Neurosci 7:357-362.

Miller EK, Erickson CA, Desimone R (1996) Neural mechanisms of visual working memory in prefrontal cortex of the macaque. J Neurosci 16:5154-5167.

Mogenson GJ (1993) From motivation to action: a review of dopamine regulation of limbic-nucleus accumbens-ventral pallidum-pedunculopontine nucleus circuitries involved in limbic-motor integration. In: Limbic Motor Circuits and Neuropsyciatry (Kalivas PW, Barnes CD, eds), pp 193–236. Boca Raton, FL: CRC Press.

Moncada D, Viola H (2007) Induction of Long-Term Memory by Exposure to Novelty Requires Protein Synthesis: Evidence for a Behavioral Tagging. J Neurosci 27:7476-7481.

Murray GK, Corlett PR, Clark L, Pessiglione M, Blackwell AD, Honey G, Jones PB, Bullmore ET, Robbins TW, Fletcher PC (2007) Substantia nigra//ventral tegmental reward prediction error disruption in psychosis. Mol Psychiatry.

Naranjo CA, Tremblay LK, Busto UE (2001) The role of the brain reward system in depression. Progress in Neuro-Psychopharmacology and Biological Psychiatry 25:781-823.

Netter P, Hennig J, Roed IS (1996) Serotonin and dopamine as mediators of sensation seeking behavior. Neuropsychobiology 34:155-165.

Nicola SM, Yun IA, Wakabayashi KT, Fields HL (2004) Cue-evoked firing of nucleus accumbens neurons encodes motivational significance during a discriminative stimulus task. J Neurophysiol 91:1840-1865.

Niv Y, Daw ND, Joel D, Dayan P (2007) Tonic dopamine: opportunity costs and the control of response vigor. Psychopharmacology (Berl) 191:507-520.

Noble EP (2000) Addiction and its reward process through polymorphisms of the D2 dopamine receptor gene: a review. Eur Psychiatry 15:79-89.

Nyberg L (2005) Any novelty in hippocampal formation and memory? Curr Opin Neurol 18:424-428.

O'Doherty J, Critchley H, Deichmann R, Dolan RJ (2003a) Dissociating valence of outcome from behavioral control in human orbital and ventral prefrontal cortices. J Neurosci 23:7931-7939.

O'Doherty JP (2004) Reward representations and reward-related learning in the human brain: insights from neuroimaging. Curr Opin Neurobiol 14:769-776.

O'Doherty JP, Hampton AN, Kim H (2007) Model-based fMRI and its application to reward-learning and decision making. Ann NY Acad Sci:annals.1390.1022.

O'Doherty JP, Dayan P, Friston K, Critchley H, Dolan RJ (2003b) Temporal difference models and reward-related learning in the human brain. Neuron 38:329-337.

O'Reilly RC, Frank MJ (2006) Making Working Memory Work: A Computational Model of Learning in the Prefrontal Cortex and Basal Ganglia. Neural Computation 18:283-328.

Ogawa S, Menon RS, Tank DW, Kim SG, Merkle H, Ellermann JM, Ugurbil K (1993) Functional brain mapping by blood oxygenation level-dependent contrast magnetic resonance imaging. A comparison of signal characteristics with a biophysical model. Biophys J 64:803-812.

Olausson P, Jentsch JD, Taylor JR (2003) Repeated nicotine exposure enhances reward-related learning in the rat. Neuropsychopharmacology 28:1264-1271.

Olds J, Milner P (1954) Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. J Comp Physiol Psychol 47:419-427.

Packard MG, Knowlton BJ (2002) LEARNING AND MEMORY FUNCTIONS OF THE BASAL GANGLIA. Annual Review of Neuroscience 25:563-593.

Pagnoni G, Zink CF, Montague PR, Berns GS (2002) Activity in human ventral striatum locked to errors of reward prediction. Nat Neurosci 5:97-98.

Panksepp J (1998) Affective Neuroscience: The Foundations of Human and Animal Emotions. New York: Oxford University Press.

Pappata S, Dehaene S, Poline JB, Gregoire MC, Jobert A, Delforge J, Frouin V, Bottlaender M, Dolle F, Di Giamberardino L, Syrota A (2002) In vivo detection of striatal dopamine release during reward: a PET study with [(11)C]raclopride and a single dynamic scan approach. Neuroimage 16:1015-1027.

Paris J (2005) Neurobiological dimensional models of personality: a review of the models of Cloninger, Depue, and Siever. J Personal Disord 19:156-170.

Parker A, Wilding E, Akerman C (1998) The Von Restorff effect in visual object recognition memory in humans and monkeys. The role of frontal/perirhinal interaction. J Cogn Neurosci 10:691-703.

Parkinson JA, Dalley JW, Cardinal RN, Bamford A, Fehnert B, Lachenal G, Rudarakanchana N, Halkerston KM, Robbins TW, Everitt BJ (2002) Nucleus accumbens dopamine depletion impairs both acquisition and performance of appetitive Pavlovian approach behaviour: implications for mesoaccumbens dopamine function. Behavioural Brain Research 137:149-163.

Pavlov IP (1927) Conditioned Reflexes: An Investigation of the Physiological Activity of the Cerebral Cortex. London: Oxford University Press.

Pessiglione M, Seymour B, Flandin G, Dolan RJ, Frith CD (2006) Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. Nature 442:1042-1045.

Petrides M (2007) The Orbitofrontal Cortex: Novelty, Deviation from Expectation, and Memory. Ann NY Acad Sci:annals.1401.1035.

Piazza PV, Maccari S, Deminiere JM, Le Moal M, Mormede P, Simon H (1991a) Corticosterone levels determine individual vulnerability to amphetamine self-administration. Proc Natl Acad Sci U S A 88:2088-2092.

Pierce RC, Crawford CA, Nonneman AJ, Mattingly BA, Bardo MT (1990) Effect of forebrain dopamine depletion on novelty-induced place preference behavior in rats. Pharmacol Biochem Behav 36:321-325.

Pietrzyk U, Herholz K, Fink G, Jacobs A, Mielke R, Slansky I, Wurker M, Heiss WD (1994) An interactive technique for three-dimensional image registration: validation for PET, SPECT, MRI and CT brain studies. J Nucl Med 35:2011-2018.

Pochon JB, Levy R, Fossati P, Lehericy S, Poline JB, Pillon B, Le Bihan D, Dubois B (2002) The neural system that bridges reward and cognition in humans: an fMRI study. Proc Natl Acad Sci U S A 99:5669-5674.

Preuschoff K, Bossaerts P, Quartz SR (2006) Neural differentiation of expected reward and risk in human subcortical structures. Neuron 51:381-390.

Rainer G, Miller EK (2000) Effects of visual experience on the representation of objects in the prefrontal cortex. Neuron 27:179-189.

Ranganath C, D'Esposito M (2001) Medial temporal lobe activity associated with active maintenance of novel information. Neuron 31:865-873.

Ranganath C, Rainer G (2003) Neural mechanisms for detecting and remembering novel events. Nat Rev Neurosci 4:193-202.

Ranganath C, Johnson MK, D'Esposito M (2000) Left anterior prefrontal activation increases with demands to recall specific perceptual information. J Neurosci 20:RC108.

Ranganath C, Johnson MK, D'Esposito M (2003) Prefrontal activity associated with working memory and episodic long-term memory. Neuropsychologia 41:378-389.

Redgrave P, Gurney K, Reynolds J (2007) What is reinforced by phasic dopamine signals? Brain Res Rev.

Ringo JL (1996) Stimulus specific adaptation in inferior temporal and medial temporal cortex of the monkey. Behavioural Brain Research 76:191-197.

Robbins TW, Everitt BJ (2007) A role for mesencephalic dopamine in activation: commentary on Berridge (2006). Psychopharmacology (Berl) 191:433-437.

Roesch MR, Olson CR (2007) Neuronal activity related to anticipated reward in frontal cortex: Does it represent value or reflect motivation? Ann NY Acad Sci:annals.1401.1004.

Rogers RD, Ramnani N, Mackay C, Wilson JL, Jezzard P, Carter CS, Smith SM (2004) Distinct portions of anterior cingulate cortex and medial prefrontal cortex are activated by reward processing in separable phases of decision-making cognition. Biological Psychiatry 55:594-602.

Rombouts SA, Barkhof F, Witter MP, Machielsen WC, Scheltens P (2001) Anterior medial temporal lobe activation during attempted retrieval of encoded visuospatial scenes: an event-related fMRI study. Neuroimage 14:67-76.

Sajikumar S, Frey JU (2004) Late-associativity, synaptic tagging, and the role of dopamine during LTP and LTD. Neurobiology of Learning and Memory 82:12-25.

Salamone JD, Correa M, Mingote SM, Weber SM (2005) Beyond the reward hypothesis: alternative functions of nucleus accumbens dopamine. Current Opinion in Pharmacology 5:34-41.

Samochowiec J, Rybakowski F, Czerski P, Zakrzewska M, Stepien G, Pelka-Wysiecka J, Horodnicki J, Rybakowski JK, Hauser J (2001) Polymorphisms in the dopamine, serotonin, and norepinephrine transporter genes and their relationship to temperamental dimensions measured by the Temperament and Character Inventory in healthy volunteers. Neuropsychobiology 43:248-253.

Santagostino G, Amoretti G, Frattini P, Zerbi F, Cucchi ML, Preda S, Corona GL (1996) Catecholaminergic, neuroendocrine and anxiety responses to acute psychological stress in healthy subjects: influence of alprazolam administration. Neuropsychobiology 34:36-43.

Saykin AJ, Johnson SC, Flashman LA, McAllister TW, Sparling M, Darcey TM, Moritz CH, Guerin SJ, Weaver J, Mamourian A (1999) Functional differentiation of medial temporal and frontal regions involved in processing novel and familiar words: an fMRI study. Brain 122:1963-1971.

Scatton B, Simon H, Le Moal M, Bischoff S (1980) Origin of dopaminergic innervation of the rat hippocampal formation. Neurosci Lett 18:125-131.

Schonberg T, Daw ND, Joel D, O'Doherty JP (2007) Reinforcement learning signals in the human striatum distinguish learners from nonlearners during reward-based decision making. J Neurosci 27:12860-12867.

Schott BH, Henson RN, Richardson-Klavehn A, Becker C, Thoma V, Heinze HJ, Duzel E (2005) Redefining implicit and explicit memory: the functional neuroanatomy of priming, remembering, and control of retrieval. Proc Natl Acad Sci U S A 102:1257-1262.

Schott BH, Niehaus L, Wittmann BC, Schutze H, Seidenbecher CI, Heinze HJ, Duzel E (2007) Ageing and early-stage Parkinson's disease affect separable neural mechanisms of mesolimbic reward processing. Brain 130:2412-2424.

Schott BH, Sellner DB, Lauer CJ, Habib R, Frey JU, Guderian S, Heinze HJ, Duzel E (2004) Activation of midbrain structures by associative novelty

and the formation of explicit memory in humans. Learn Mem 11:383-387.

Schott BH, Seidenbecher CI, Fenker DB, Lauer CJ, Bunzeck N, Bernstein HG, Tischmeyer W, Gundelfinger ED, Heinze HJ, Duzel E (2006) The dopaminergic midbrain participates in human episodic memory formation: evidence from genetic imaging. J Neurosci 26:1407-1417.

Schultz W (1997) Dopamine neurons and their role in reward mechanisms. Curr Opin Neurobiol 7:191-197.

Schultz W (1998) The phasic reward signal of primate dopamine neurons. Adv Pharmacol 42:686-690.

Schultz W (2002) Getting formal with dopamine and reward. Neuron 36:241-263.

Schultz W (2004) Neural coding of basic reward terms of animal learning theory, game theory, microeconomics and behavioural ecology. Curr Opin Neurobiol 14:139-147.

Schultz W, Tremblay L, Hollerman JR (1998) Reward prediction in primate basal ganglia and frontal cortex. Neuropharmacology 37:421-429.

Scott DJ, Stohler CS, Egnatuk CM, Wang H, Koeppe RA, Zubieta J-K (2007) Individual Differences in Reward Responding Explain Placebo-Induced Expectations and Effects. Neuron 55:325-336.

Shenton ME, Dickey CC, Frumin M, McCarley RW (2001) A review of MRI findings in schizophrenia. Schizophr Res 49:1-52.

Shumake J, Barrett D, Gonzalez-Lima F (2005) Behavioral characteristics of rats predisposed to learned helplessness: reduced reward sensitivity, increased novelty seeking, and persistent fear memories. Behav Brain Res 164:222-230.

Skinner BF (1958) Diagramming schedules of reinforcement. J Exp Anal Behav 1:67-68.

Sobotka S, Ringo JL (1994) Stimulus specific adaptation in excited but not in inhibited cells in inferotemporal cortex of macaque. Brain Res 646:95-99.

Sokolov EN (1963) Higher nervous functions; the orienting reflex. Annu Rev Physiol 25:545-580.

Sokolov EN, Nezlina NI, Polyanskii VB, Evtikhin DV (2002) The orientating reflex: the "targeting reaction" and "searchlight of attention". Neurosci Behav Physiol 32:347-362.

Spicer J, Galvan A, Hare TA, Voss H, Glover G, Casey B (2007) Sensitivity of the nucleus accumbens to violations in expectation of reward. Neuroimage 34:455-461.

Squire LR, Clark RE, Bayley PJ (2004) Medial Temporal Lobe Function and Memory. In: The Cognitive Neurosciences III (3rd ed.) (Gazzaniga MS, ed). Cambridge, MA: MIT Press.

Squires NK, Squires KC, Hillyard SA (1975) Two varieties of long-latency positive waves evoked by unpredictable auditory stimuli in man. Electroencephalogr Clin Neurophysiol 38:387-401.

Stark CE, McClelland JL (2000) Repetition priming of words, pseudowords, and nonwords. J Exp Psychol Learn Mem Cogn 26:945-972.

Stead JD, Clinton S, Neal C, Schneider J, Jama A, Miller S, Vazquez DM, Watson SJ, Akil H (2006) Selective breeding for divergence in novelty-

seeking traits: heritability and enrichment in spontaneous anxiety-related behaviors. Behav Genet 36:697-712.

Stellar JR, Stellar E (1985) The neurobiology of motivation and reward. New York: Springer Verlag.

Stern CE, Corkin S, Gonzalez RG, Guimaraes AR, Baker JR, Jennings PJ, Carr CA, Sugiura RM, Vedantham V, Rosen BR (1996) The hippocampal formation participates in novel picture encoding: evidence from functional magnetic resonance imaging. Proc Natl Acad Sci U S A 93:8660-8665.

Strange BA, Dolan RJ (2001) Adaptive anterior hippocampal responses to oddball stimuli. Hippocampus 11:690-698.

Strange BA, Duggins A, Penny W, Dolan RJ, Friston KJ (2005) Information theory, novelty and hippocampal responses: unpredicted or unpredictable? Neural Netw 18:225-230.

Strohle A, Stoy M, Wrase J, Schwarzer S, Schlagenhauf F, Huss M, Hein J, Nedderhut A, Neumann B, Gregor A, Juckel G, Knutson B, Lehmkuhl U, Bauer M, Heinz A (2008) Reward anticipation and outcomes in adult males with attention-deficit/hyperactivity disorder. Neuroimage 39:966-972.

Stuettgen MC, Hennig J, Reuter M, Netter P (2005) Novelty Seeking but not BAS is associated with high dopamine as indicated by a neurotransmitter challenge test using mazindol as a challenge substance. Personality and Individual Differences 38:1597-1608.

Sutton RS (1998) Reinforcement learning: An introduction. Cambridge, MA: MIT Press.

Sutton S, Braren M, Zubin J, John ER (1965) Evoked-potential correlates of stimulus uncertainty. Science 150:1187-1188.

Suwazono S, Machado L, Knight RT (2000) Predictive value of novel stimuli modifies visual event-related potentials and behavior. Clin Neurophysiol 111:29-39.

Thiel CM, Henson RN, Dolan RJ (2002) Scopolamine but not lorazepam modulates face repetition priming: a psychopharmacological fMRI study. Neuropsychopharmacology 27:282-292.

Thiel CM, Henson RN, Morris JS, Friston KJ, Dolan RJ (2001) Pharmacological modulation of behavioral and neuronal correlates of repetition priming. J Neurosci 21:6846-6852.

Thut G, Schultz W, Roelcke U, Nienhusmeier M, Missimer J, Maguire RP, Leenders KL (1997) Activation of the human brain by monetary reward. Neuroreport 8:1225-1228.

Tran AH, Tamura R, Uwano T, Kobayashi T, Katsuki M, Matsumoto G, Ono T (2002) Altered accumbens neural response to prediction of reward associated with place in dopamine D2 receptor knockout mice. Proc Natl Acad Sci U S A 99:8986-8991.

Tulving E, Markowitsch HJ, Kapur S, Habib R, Houle S (1994) Novelty encoding networks in the human brain: positron emission tomography data. Neuroreport 5:2525-2528.

Tulving E, Markowitsch HJ, Craik FE, Habib R, Houle S (1996) Novelty and familiarity activations in PET studies of memory encoding and retrieval. Cereb Cortex 6:71-79.

Vallone D, Picetti R, Borrelli E (2000) Structure and function of dopamine receptors. Neuroscience and Biobehavioral Reviews 24:125-132.

van Ree JM, Gerrits MA, Vanderschuren LJ (1999) Opioids, reward and addiction: An encounter of biology, psychology, and medicine. Pharmacol Rev 51:341-396.

Vargha-Khadem F, Gadian DG, Watkins KE, Connelly A, Van Paesschen W, Mishkin M (1997) Differential effects of early hippocampal pathology on episodic and semantic memory. Science 277:376-380.

Ventura R, Morrone C, Puglisi-Allegra S (2007) Prefrontal/accumbal catecholamine system determines motivational salience attribution to both reward- and aversion-related stimuli. PNAS:0610178104.

Ventura R, Cabib S, Alcaro A, Orsini C, Puglisi-Allegra S (2003) Norepinephrine in the prefrontal cortex is critical for amphetamine-induced reward and mesoaccumbens dopamine release. J Neurosci 23:1879-1885.

Vinogradova OS (2001) Hippocampus as comparator: role of the two input and two output systems of the hippocampus in selection and registration of information. Hippocampus 11:578-598.

Vollmayr B, Bachteler D, Vengeliene V, Gass P, Spanagel R, Henn F (2004) Rats with congenital learned helplessness respond less to sucrose but show no deficits in activity or learning. Behav Brain Res 150:217-221.

von Restorff H (1933) Über die Wirkung von Bereichsbildungen im Spurenfeld. Psychological Research 18:299-342.

Wagner HN, Jr., Burns HD, Dannals RF, Wong DF, Langstrom B, Duelfer T, Frost JJ, Ravert HT, Links JM, Rosenbloom SB, Lukas SE, Kramer AV, Kuhar MJ (1983) Imaging dopamine receptors in the human brain by positron tomography. Science 221:1264-1266.

Wan H, Aggleton JP, Brown MW (1999) Different contributions of the hippocampus and perirhinal cortex to recognition memory. J Neurosci 19:1142-1148.

Weiler JA, Bellebaum C, Daum I (2008) Aging affects acquisition and reversal of reward-based associative learning. Learn Mem 15:190-197.

Wiggs CL, Martin A (1998) Properties and mechanisms of perceptual priming. Current Opinion in Neurobiology 8:227-233.

Willner P, Towell A, Sampson D, Sophokleous S, Muscat R (1987) Reduction of sucrose preference by chronic unpredictable mild stress, and its restoration by a tricyclic antidepressant. Psychopharmacology (Berl) 93:358-364.

Wills TA, Vaccaro D, McNamara G (1994) Novelty seeking, risk taking, and related constructs as predictors of adolescent substance use: An application of Cloninger's theory. Journal of Substance Abuse 6:1-20.

Wittmann BC, Bunzeck N, Dolan RJ, Duzel E (2007) Anticipation of novelty recruits reward system and hippocampus while promoting recollection. Neuroimage 38:194-202.

Wittmann BC, Schiltz K, Boehler CN, Duzel E (2008) Mesolimbic interaction of emotional valence and reward improves memory formation. Neuropsychologia 46:1000-1008.

Wittmann BC, Schott BH, Guderian S, Frey JU, Heinze HJ, Duzel E (2005) Reward-related FMRI activation of dopaminergic midbrain is associated

with enhanced hippocampus-dependent long-term memory formation. Neuron 45:459-467.

Wu M, Brudzynski SM, Mogenson GJ (1993) Functional interaction of dopamine and glutamate in the nucleus accumbens in the regulation of locomotion. Can J Physiol Pharmacol 71:407-413.

Yacubian J, Sommer T, Schroeder K, Glascher J, Kalisch R, Leuenberger B, Braus DF, Buchel C (2007) Gene-gene interaction associated with neural reward sensitivity. PNAS 104:8125-8130.

Yamaguchi S, Hale LA, D'Esposito M, Knight RT (2004) Rapid prefrontal-hippocampal habituation to novel events. J Neurosci 24:5356-5363.

Yun IA, Wakabayashi KT, Fields HL, Nicola SM (2004) The Ventral Tegmental Area Is Required for the Behavioral and Nucleus Accumbens Neuronal Firing Responses to Incentive Cues. J Neurosci 24:2923-2933.

Zald DH, Boileau I, El-Dearedy W, Gunn R, McGlone F, Dichter GS, Dagher A (2004) Dopamine transmission in the human striatum during monetary reward tasks. J Neurosci 24:4105-4112.

Zimmermann A, Stauffacher M, Langhans W, Wurbel H (2001) Enrichment-dependent differences in novelty exploration in rats can be explained by habituation. Behav Brain Res 121:11-20.

Zink CF, Pagnoni G, Martin-Skurski ME, Chappelow JC, Berns GS (2004) Human striatal responses to monetary reward depend on saliency. Neuron 42:509-517.

Zola-Morgan S, Squire LR, Amaral DG, Suzuki WA (1989) Lesions of perirhinal and parahippocampal cortex that spare the amygdala and hippocampal formation produce severe memory impairment. J Neurosci 9:4355-4370.

Zuckerman M, Kuhlman DM (2000) Personality and Risk-Taking: Common Bisocial Factors. Journal of Personality 68:999-1029.

9. Appendix

A Supplemental tables Exp 1 and 2

Tab. a1. Temperament scales of interest (taken from TCI)

Reward dependence (RewD)	
RewD 1	*sentimentality*
RewD 2	*persistence*
RewD 3	*attachment*
RewD 4	*dependence*
Reward dependence+ (RewD+)	
RewD 1	sentimentality
RewD 3	*attachment*
RewD 4	*dependence*
Novelty Seeking(NovS)	
NovS 1	*exploratory excitability (ExpE)*
NovS 2	*impulsiveness*
NovS 3	*extravagance*
NovS 4	*disorderliness*
Harm Avoidance (HarmA)	
HarA 1	*anticipatory worry*
HarA 2	*fear of uncertainty*
HarA 3	*shyness with strangers*
HarA 4	*fatigability and asthenia*

TCI: Temperament and Character Inventory (by Cloninger 1991, 1994)
RewD+: alternative score since *persistence* had been denoted as independent factor

Tab. a2. Activation table for reward-predicting cues in Exp 1 (novelty/familiarity independent)

region	left/right	peak coordinates			t-value
		x	*y*	*z*	
Contrast reward vs. neutral					
cingulate ctx	left	-1	-3	54	7.11
cingulate ctx	right	3	-6	57	7.42
NAcc	left	-12	15	-9	6.77
NAcc	right	9	15	-3	5.98
prefrontal ctx	left	-33	36	45	6.13
prefrontal ctx	right	36	36	45	5.07
caudate nucleus	left	-12	-6	15	5.66
caudate nucleus	right	12	-18	19	4.58
lateral occipital ctx	left	-22	-90	-15	5.20
lateral occipital ctx	right	27	-81	-15	5.43
parietal ctx	left	-33	-63	57	5.52
parietal ctx	right	33	-63	63	3.08
putamen	left	-21	12	-9	4.78
putamen	right	21	12	-6	4.45
medial occipital ctx	left	-3	-57	9	4.27
medial occipital ctx	right	3	-57	9	4.21
orbitofrontal ctx	left	-6	42	-6	4.02
orbitofrontal ctx	right	9	33	-12	3.15
hippocampus/parahip. region	left	-18	-21	-18	4.00
hippocampus/parahip. region	right	24	-18	-21	3.74
SN/VTA	right	6	-21	-12	3.80
SN/VTA	left	-3	-21	-21	3.03

All values are thresholded at p=.005, k=5
ctx: cortex

Tab. a3. Activation tables for novel and familiar cues in Exp 1 (reward independent)

region	left/right	peak coordinates			t-value
		x	*y*	*z*	
Contrast novel vs. familiar					
medial occipital ctx	left	-9	-78	12	6.33
medial occipital ctx	right	15	-78	12	7.06
fusiform gyrus	left	-27	-48	-6	4.81
fusiform gyrus	right	30	-48	-9	4.93
lateral occipital ctx	left	-30	-81	21	4.49
lateral occipital ctx	right	33	-75	24	4.42
dorsal anterior cingulate ctx	left	-3	15	39	3.77
dorsal anterior cingulate ctx	right	3	21	39	3.47
parietal ctx	right	45	-15	42	3.31
Contrast familiar vs. novel					
superior parietal ctx	left	-48	-54	51	5.03
superior parietal ctx	right	42	-66	39	4.71
parietal ctx	left	-9	-51	30	4.89
parietal ctx	right	6	-54	24	4.05
medial prefrontal ctx	left	-6	57	3	4.59
medial prefrontal ctx	right	3	57	0	3.21
temporal ctx	left	-60	-51	-6	4.36
temporal ctx	right	69	-45	3	3.48
lateral prefrontal ctx	left	-54	30	21	4.30

All values are thresholded at p=.005, k=5
ctx: cortex

Tab. a4. Activation table for familiar reward-predicting cues in Exp 1

region	left/right	peak coordinates			t-value
		x	*y*	*z*	
caudate nucleus	right	9	9	6	7.16
caudate nucleus	left	-12	-6	18	6.27
NAcc	right	9	9	-9	7.21
NAcc	left	-6	12	-9	6.44
superior parietal ctx	left	-30	-63	57	5.97
thalamus	right	15	-21	9	4.98
thalamus	left	-6	-24	9	3.95
lateral frontal ctx	left	-30	36	45	4.88
medial frontal ctx	left	-6	48	3	4.48
putamen	left	-18	9	3	4.70
putamen	right	21	6	3	3.76
SN/VTA	left	-7	-18	-16	3.02
SN/VTA	right	11	-17	-16	3.02

All values are thresholded at p=.005, k=5
ctx: cortex

Tab. a5. Activation tables for positive outcome in Exp 1

region	left/right	peak coordinates			t-value
		x	*y*	*z*	
Contrast gain vs. neutral					
anterior insula	right	39	21	-9	11.23
anterior insula	left	-30	21	-15	9.57
anterior cingulate ctx	right	3	39	18	9.68
fusiform gyrus	right	30	-63	-9	7.51
fusiform gyrus	left	-27	-63	-9	5.07
occipital ctx	right	24	-87	-12	7.40
occipital ctx	left	-24	-87	-9	4.45
thalamus	right	6	-6	6	5.97
SN/VTA	left	-3	-18	-21	5.40
lateral prefrontal ctx	right	39	48	24	4.06
Contrast novel-gain vs. familiar-gain					
anterior insula	right	36	24	-6	5.73
SN/VTA	left	-9	-15	-18	3.45
SN/VTA	right	6	-9	-9	3.93
NAcc	right	12	6	-3	3.30
NAcc	left	-9	9	-3	2.89
Contrast familiar-gain vs. novel-gain					
occipital ctx	left	-2	-81	15	4.86
parietal/temporal ctx	left	-60	-21	9	5.29
parietal/temporal ctx	right	63	-33	12	4.42

All values are thresholded at p=0.005, k=5
ctx: cortex

Tab. a6. Activation table for reward-predicting cues in Exp 2 (novelty/familiarity independent)

	left/right	peak coordinates			t-value
		x	*y*	*z*	
Contrast reward vs. neutral					
NAcc	left	-15	15	-12	4.76
NAcc	right	15	15	-12	7.14
cingulate ctx	left	-3	9	48	6.75
cingulate ctx	right	3	9	48	4.88
putamen	left	-21	12	-9	6.54
putamen	right	21	12	-3	5.42
medial occipital ctx	left	-3	-60	6	5.76
medial occipital ctx	right	6	57	9	5.91
lateral occipital ctx	left	-36	-84	-15	4.54
lateral occipital ctx	right	36	-90	-12	5.41
parietal ctx	left	-6	-75	51	5.32
parietal ctx	right	6	-72	51	4.61
SN/VTA	left	-6	-21	-12	5.36
SN/VTA	right	6	-15	-15	3.65
hippocampus/parahip. region	right	21	-18	-18	4.68
lateral prefrontal ctx	left	-36	51	27	4.38
lateral prefrontal ctx	right	33	45	36	4.38
caudate nucleus	left	-9	-3	12	4.24
caudate nucleus	right	12	3	12	4.37
medial prefrontal ctx	left	-2	60	15	5.76

All values are thresholded at p=0.005, k=5
ctx: cortex

Tab. a7. Activation tables for novel and familiar cues in Exp 2 (reward independent)

region	left/right	peak coordinates			t-value
		x	*y*	*z*	
Contrast novel vs. familiar					
precentral gyrus	left	-45	-9	60	5.81
precentral gyrus	right	36	-36	54	4.82
insula	left	-39	-6	15	5.13
insula	right	39	0	9	4.86
prefrontal ctx	right	24	51	-9	4.66
thalamus	right	15	-15	-3	4.46
amygdala	left	-21	-3	-30	3.68
amygdala	right	24	0	-27	4.41
fusiform gyrus	right	24	-51	-6	4.19
parietal/occipital ctx	right	45	-39	18	4.10
SN/VTA	right	18	-12	-12	3.54
hippocampus	left	-24	-15	-12	3.13
Contrast familiar vs. novel					
superior parietal ctx	left	-6	-66	51	3.89
superior parietal ctx	right	6	-69	48	2.00
lateral prefrontal ctx	left	-42	48	0	3.84
parietal ctx	left	-27	-72	48	3.68
occipital ctx	left	-9	-99	6	3.22

All values are thresholded at p=0.005, k=5
ctx: cortex

Tab. a8. Activation table for novel reward-predicting cues in Exp 2

region	left/right	peak coordinates			t-value
		x	*y*	*z*	
putamen	left	-21	12	3	7.26
putamen	right	24	12	-3	6.15
occipital ctx	right	3	-63	6	7.10
occipital ctx	left	-9	-66	12	5.63
NAcc	left	-6	12	-6	5.61
NAcc	right	18	15	-15	6.44
anterior cingulate ctx	left	-3	9	48	6.20
anterior cingulate ctx	right	3	15	48	5.56
precentral gyrus	left	-48	-12	51	6.23
lateral frontal ctx	left	-42	33	36	5.03
lateral frontal ctx	right	30	45	36	4.32
SN/VTA	left	-6	-18	-17	4.17
SN/VTA	right	8	-17	-17	3.57
hippocampus	right	27	-18	-15	3.30

All values are thresholded at p=0.005, k=5
ctx: cortex

Tab. a9: Activation tables for positive outcome in Exp 2

region	left/right	peak coordinates			t-value
		x	*y*	*z*	
Contrast gain vs. neutral					
anterior insula	right	33	24	-3	7.57
anterior insula	left	-33	15	-18	5.84
fusiform gyrus	right	27	-60	-12	7.47
fusiform gyrus	left	-27	-48	-18	4.81
lateral prefrontal ctx	right	42	36	-3	7.39
anterior cingulate ctx	right	6	30	39	6.51
occipital ctx	right	21	-93	-9	6.36
occipital ctx	left	-24	-90	-9	6.25
thalamus	right	6	-15	12	4.88
SN/VTA	right	9	-21	-18	4.46
Contrast novel-gain vs. familiar-gain					
occipital ctx	left	-12	-90	-15	3.91
thalamus	left	-6	-18	9	3.73
thalamus	right	6	-15	9	3.42
Contrast familiar-gain vs. novel-gain					
amygdala	right	21	-3	-27	4.74
parahippocampal region	right	36	-18	-27	4.34
fusiform gyrus	left	-27	-39	-18	3.76

All values are thresholded at p=0.005, k=5
ctx: cortex

Table a10. Correlations between BOLD signal change within regions of interest and *ExpE/RewD+*

	SN/VTA right				**NAcc right**				***Hippocampus right***			
	novel cues		familiar cues		novel cue		familiar cues		novel cues		familiar cues	
	rew	neut	rew	neut	rew	neut	rew	neut	rew	neut	rew	neut
ExpE	.30	**.56***	.14	.36	.12	.23	-.11	.11	-.42	-.34	**-.57***	-.19
r (p)	(.114)	**(.002)**	(.479)	(.052)	(.549)	(.215)	(.561)	(.575)	(.024)	(.072)	**(.001)**	(.312)
RewD+	**.57***	.33	.38	.32	.42	.41	.33	.48	-.44	-.08	-.52	-.13
r (p)	**(.001)**	(.079)	(.044)	(.089)	(.023)	.029)	(.080)	(.009)	(.016)	(.684)	(.004)	(.513)

	SN/VTA left				**NAcc left**				**Hippocampus left**			
	novel cues		familiar cues		novel cue		familiar cues		novel cues		familiar cues	
	rew	neut	rew	neut	rew	neut	rew	neut	rew	neut	rew	neut
ExpE	-.33	.15	-.32	.14	.08	.19	.05	.36	-.28	-.15	-.34	-.30
r (p)	(.081)	(.431)	(.094)	(.478)	(.664)	(.333)	(.796)	(.053)	(.137)	(.433)	(.069)	(.109)
RewD+	-.08	.04	-.04	.26	.20	.18	24	.19	-.34	-.13	-.46	-.23
r (p)	(.675)	(.855)	(.832)	(.176)	(.296)	(.360)	(.216)	(.320)	(.073)	(.503)	(.011)	(.228)

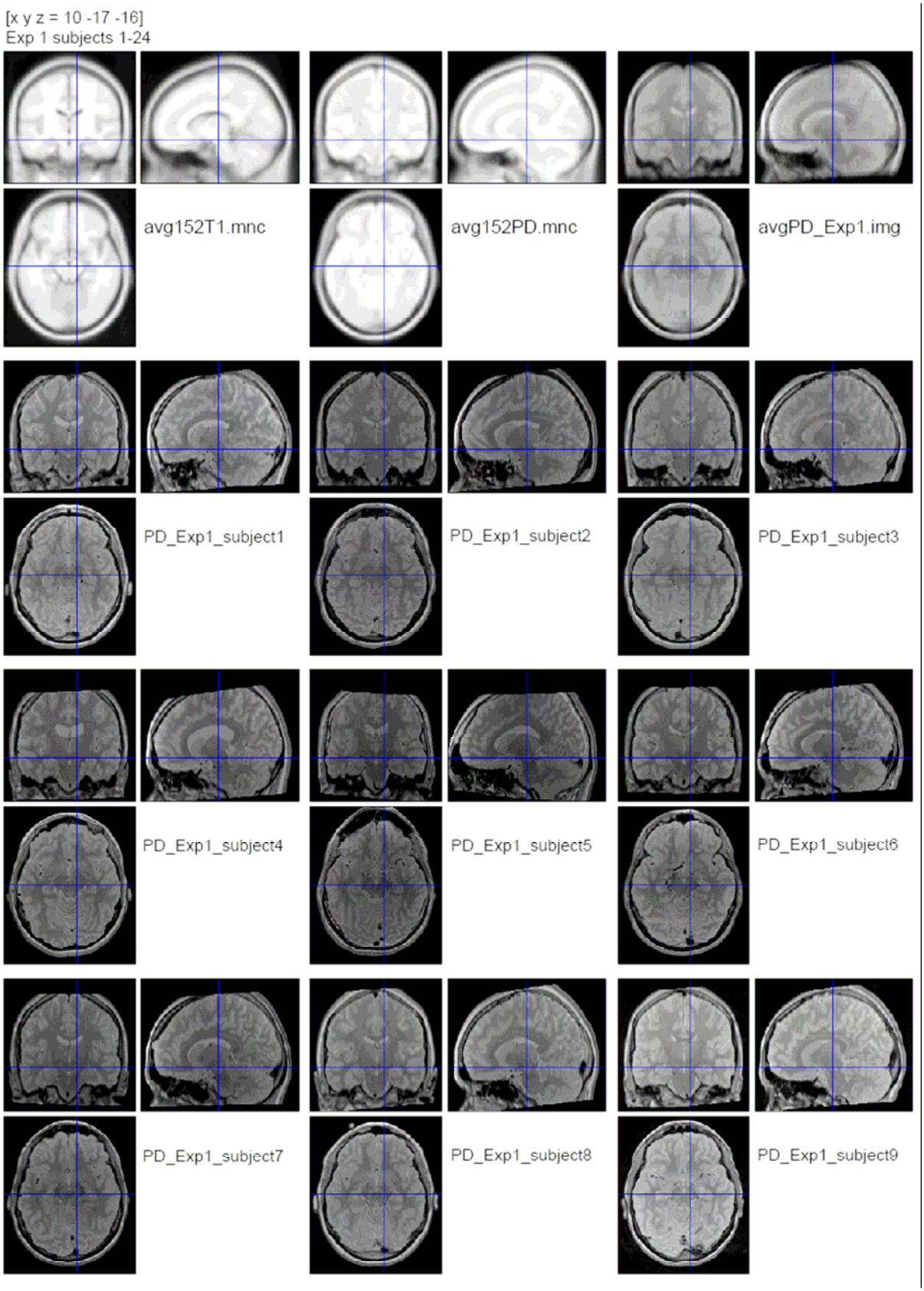
rew: reward-predicting cues
neut: neutral cues
r: correlation coefficient (Pearson)
* significance threshold **p** < .002 (two-tailed)

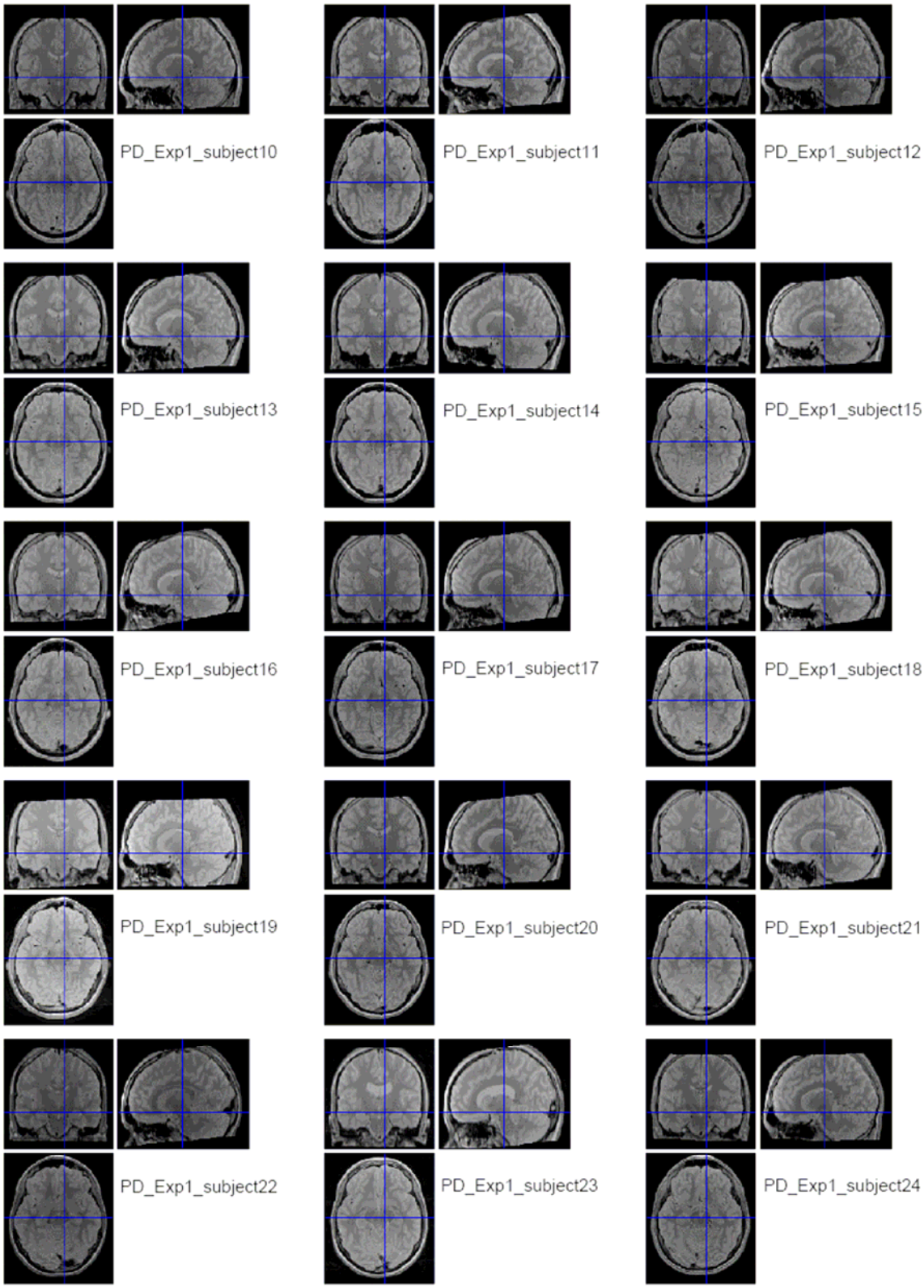
Table a11. Correlations between recollection rate and *ExpE/RewD+*

	Recollection rate					
	Novel cues			Familiar cues		
	rew	neut	diff	rew	neut	diff
ExpE	-.11	.15	**-.43***	-.13	-.10	-.04
r (p)	(563)	(.425)	**(.021)**	(520)	(.600)	(821)
RewD+	.11	.19	-.10	.36	.19	.23
r (p)	(564)	(.334)	(.615)	(.057)	(318)	(221)

rew: reward-predicting cues
neut: neutral cues
diff: reward-predicting minus neutral cues
r: correlation coefficient (Pearson)
* significance threshold **p** < .025 (two-tailed)

B Registration check for Normalization experiments 1 and 2

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PD_Exp1_subject11
PD_Exp1_subject12
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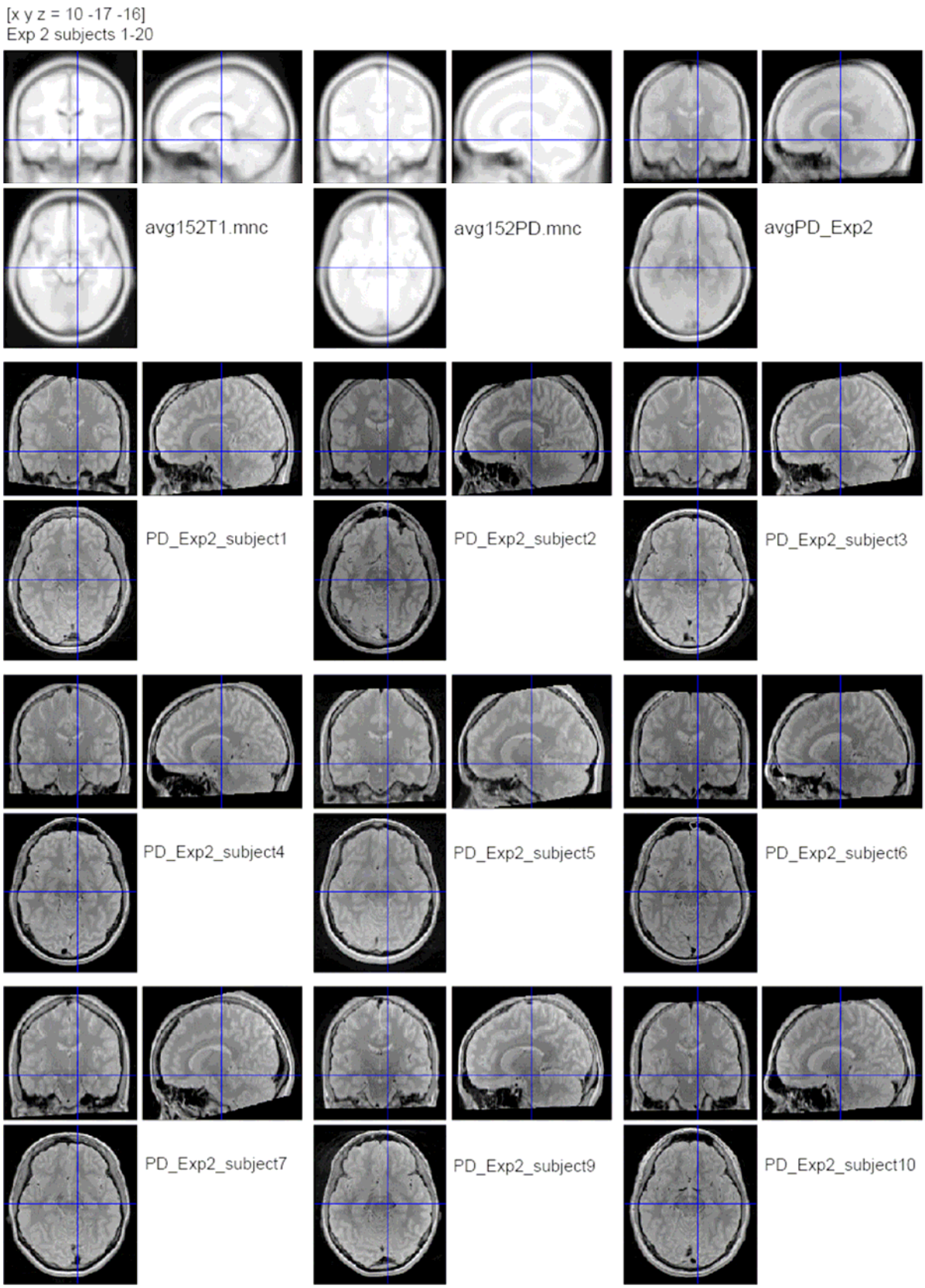
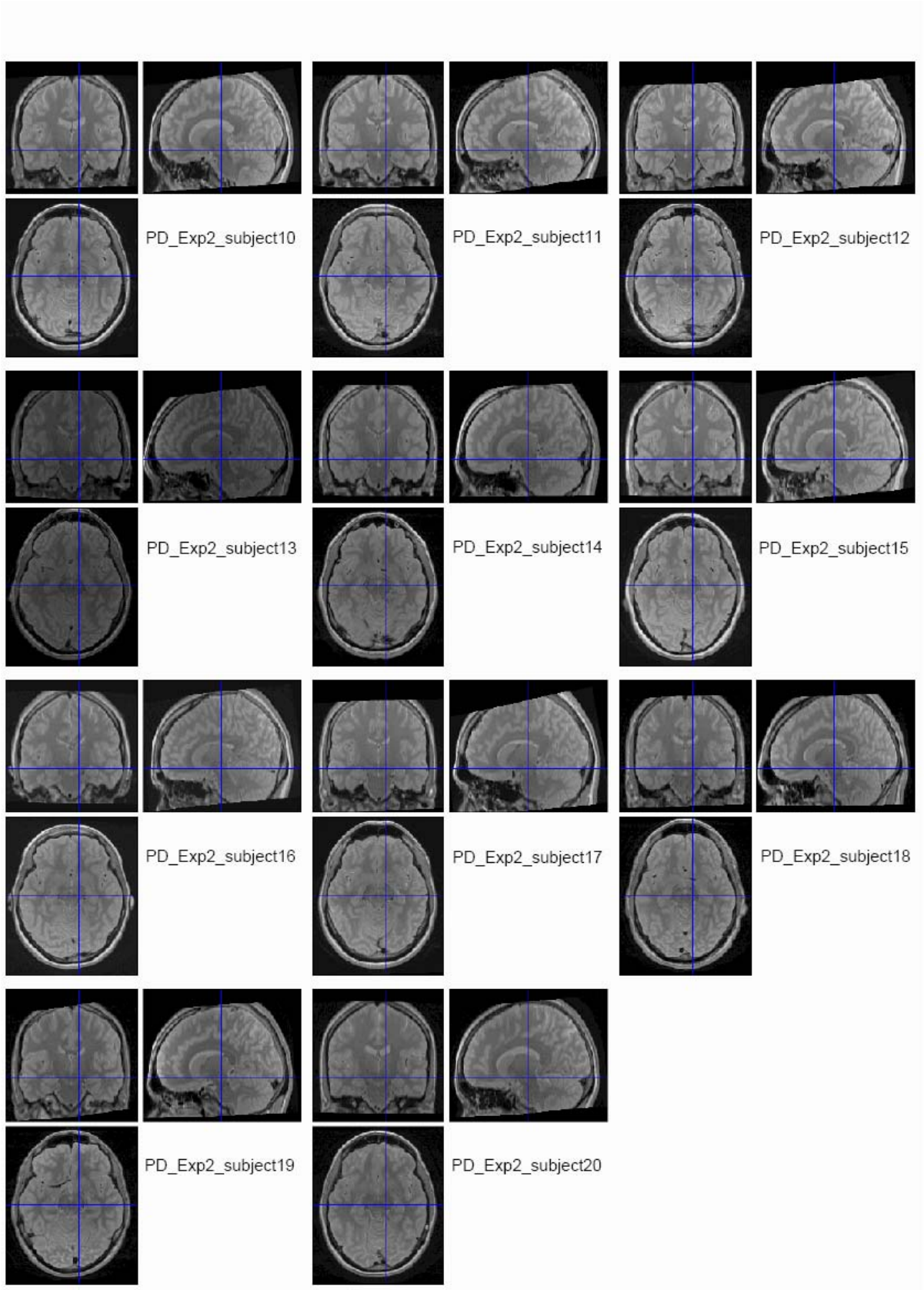
PD_Exp1_subject22
PD_Exp1_subject23
PD_Exp1_subject24


[x y z = 10 -17 -16]
Exp 2 subjects 1-20
avg152T1.mnc
avg152PD.mnc
avgPD_Exp2
PD_Exp2_subject1
PD_Exp2_subject2
PD_Exp2_subject3
PD_Exp2_subject4
PD_Exp2_subject5
PD_Exp2_subject6
PD_Exp2_subject7
PD_Exp2_subject9
PD_Exp2_subject10


PD_Exp2_subject10
PD_Exp2_subject11
PD_Exp2_subject12
PD_Exp2_subject13
PD_Exp2_subject14
PD_Exp2_subject15
PD_Exp2_subject16
PD_Exp2_subject17
PD_Exp2_subject18
PD_Exp2_subject19
PD_Exp2_subject20

C [^{11}C]raclopride synthesis Exp 3

The [^{11}C]Raclopride synthesis was carried out by M. Lang at the Institute of Medicine, Research Center Jülich.

Raclopride and norraclopride (free base) were commercially available from ABX (Radeberg, Germany). Methanol was dried by destillation from magnesium turnings under argon. Li-methylate was obtained from Aldrich (Taufkirchen, Germany). All other chemicals and solvents were purchased from Merck (Darmstadt, Germany) and were used as delivered by the vendor. The benzamide [^{11}C]raclopride was prepared at high specific radioactivity as described elsewhere (Stuesgen et al. 2007). Briefly, n.c.a. [^{11}C]methyl iodide was synthesized according to a published procedure (Holschbach et al. 1993). Analytical radio high performance liquid chromatography (HPLC) employed a Kromasil 100-5 C18 column (250 x 4.6 mm). Isocratic elution with CH_3CN / .006 N H_3PO_4 + NaH_2PO_4 x $2H_2O$ (7.9 g / L eluent), 35 / 65 (v / v) was at a flow rate of 1 mL / min. UV monitoring at 210 nm detected raclopride and side products. For measurement of radioactivity the outflow of the UV detector was connected in series to an on-line NaI(Tl) well-type scintillation detector. Chromatograms were corrected for the transit time between the detectors. Semi-preparative HPLC was performed on a Kromasil 100-5 C18 column (250 x 8 mm). Isocratic elution with CH_3CN / .006 N H_3PO_4 + NaH_2PO_4 x $2H_2O$ (22.6 g / L eluent), 28 / 72 (v / v) was at a flow rate of 5 mL / min with UV detection at 210 nm. For solid phase extraction Sep Pak cartridges (Waters Oasis HLB 60 mg) were preconditioned with EtOH (10 mL) and water (10 mL). The lithium phenoxide precursor-salt was prepared by dissolving norraclopride (the free amine) in three molar equivalents of .1M methanolic LiOMe followed by evaporation to dryness under a stream of helium. The formed glassy solid of the lithium phenolate was dissolved in DMF (500 µL) and immediately subjected to methylation (80°C, 3 min) followed by helium gas purge (80°C, 2 min). The reaction mixture was subjected to semi-preparative HPLC, the fraction containing the product was collected, diluted with water (90 mL) and the product was purified by solid phase extraction. Elution of the tracer with EtOH, dilution with isotonic saline and filtration through a sterile filter gave [^{11}C]Raclopride ready for injection.

References:

Holschbach, M., and Schüller, M. (1993). A new and simple on-line method for the preparation of n.c.a. [11C]methyl iodide. Appl Radiat Isot *44*, 779-780.

Stüsgen, S., Lang, M., and Bier, D. (2007). A new and reliable radiosynthesis of of n.c.a. [11C]raclopride. Labelled Cpd Radiopharm *50*, 173.

Curriculum Vitae

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Name:	Ruth Marie Krebs
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University Education

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April 2004 – October 2005	Postgraduate studies in Psychological Neuroscience at the Justus-Liebig-University, Gießen Major subject: Psychoneuroimmunology
October 1998 – October 2004	Psychology at the Justus-Liebig-University, Gießen Diploma thesis: Aggression and its developmental conditions Additional subjects: Neuroanatomy, Forensic Psychology

School Education

1995 – 1998	Highschool Diploma at the Laubach-Kolleg
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