Cognitive regulation effects on neural responses to reward and drug-conditioned cues in healthy participants and current smokers

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Hiermit erkläre ich, dass ich die vorliegende Arbeit selbständig und ohne fremde Hilfe verfasst und nur die angegeben Hilfsmittel und Quellen benutzt habe. Weiterhin erkläre ich, dass die Dissertation weder in Teilen noch in ihrer Gesamtheit einer anderen wissenschaftlichen Hochschule zur Begutachtung in einem Promotionsverfahren vorliegt noch vorgelegen hat.

Hamburg, den _____ _____

Markus R. Staudinger

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To Klaus

I love you

We’ll meet again

Contents

Summary

To work successfully, to relate to others in a satisfying way, or to have a rich inner life, we have to be able to produce and express positive feelings. Sometimes however, we have to regulate immediate positive feelings in order to be able to pursue "better" actions, that is, actions that will lead to delayed beneficial outcomes or avoid detrimental ones. For instance, we may regulate our desire for delicious high-fat food for the sake of health in old age. Thus, emotion regulation (ER) contributes to the preservation of mental and bodily health. Conversely, the inability to regulate pathological desire for rewarding drugs is a central characteristic of addictive disorders such as nicotine addiction. It is therefore imperative to determine why some people are able to regulate their desire for rewards while others are not. Furthermore, could smokers benefit from ER training during the regulation of craving and manage to abstain? In this dissertation, I used functional magnetic resonance imaging (fMRI) to investigate three important questions: (a) Is the ER strategy of distancing suited to regulate reward-related desire and motivation as well as neural signals that underlie the computation of reward? (b) What are the neural processes that underpin successful regulation of reward? (c) Can smokers learn to use ER to successfully regulate both craving and neural smoking cue responses?

In study I, I show that healthy subjects are able to use distancing to diminish feelings of reward anticipation and pleasure in the context of monetary reward. Furthermore, I demonstrate that although distancing primarily aims at the reduction of reward-related emotion experience, it also diminishes ventral striatal signals that underlie the expectation (i.e., expected value signals) and evaluation (i.e., prediction error signals) of reward. These results suggest that healthy subjects that are willing to modify disagreeable reward-related behavior—for instance, the excessive consumption of sweets—may use distancing to reduce expected value signals pertaining to reward predicting cues (e.g., the sight of a chocolate bar) and may thus diminish their craving for reward. Furthermore, the ER effects on reward prediction errors suggest that even if healthy subjects would not resist the temptation to consume reward, they could still

influence how much pleasure they would experience during reward consumption. Distancing-related modulation of prediction error signals would therefore be an option to alter reward values indirectly.

In study II, I can show that distancing from monetary reward not only diminishes feelings of reward anticipation and pleasure, but also behaviorally measurable motivation to obtain reward. Moreover, I provide evidence that the putamen is one brain region where such reward motivation is converted into action and that distancing prevents such conversion via modulation of the putamen. Finally, I demonstrate that successful regulation of neural expected value encoding is partly mediated by DLPFC modulation of the putamen. In sum, the results of study II show that ER can reduce behavioral and neural markers of the motivation to obtain reward which I consider a conditio sine qua non for ER being a promising tool to prevent drug *pursuit*. Furthermore, the results shed further light on the mechanisms of prefrontal-subcortical interactions during ER, extending previous findings about DLPFC's involvement in the regulation of amygdala signals in aversive contexts to the domain of reward regulation.

In study III, I can show that both satiated and overnight abstinent smokers can use distancing to regulate craving for smoking when they are exposed to smoking cues in a safe laboratory environment. Moreover, degree of nicotine dependence does not seem to impair this ability to regulate craving via distancing. At the neural level, I demonstrate that distancing reduces neural responses to smoking cues in smoking status-independent (VMPFC) as well as in abstinence-specific (caudate, amygdala, and subgenual ACC) brain regions that have been associated with motivational aspects of nicotine addiction such as drug craving or drug valuation. However, I also show that in the left caudate, ER-related reductions of smoking cue responses decreased with increasing degree of nicotine dependence. In sum, the results of study III suggest that smokers can really be trained to use ER skills to control craving for smoking as well as neural smoking cue responses in addiction-relevant areas, as is already attempted in interventions such as cue exposure treatment. Future studies have to investigate whether such effects are replicable under field conditions, where smoking cues are omnipresent and cigarettes are available. Furthermore, given the current theories on caudate involvement in goal-directed action and value computation, I suppose that prolonged abstinence may induce

a temporary state in heavy smokers in which they cannot readily use shortly-trained ER skills to devaluate smoking cues.

Zusammenfassung

Die Fähigkeit positive Gefühle hervorzubringen und ausdrücken zu können ist eine unerlässliche Voraussetzung um erfolgreich zu arbeiten, befriedigende soziale Beziehungen zu unterhalten, oder ein reichhaltiges Innenleben zu kultivieren. Von Zeit zu Zeit jedoch ist es notwendig, dass wir unseren spontanen positiven Gefühlen nicht nachgeben, damit wir Handlungen vollziehen können, die uns auf längere Frist vorteilhaftere Ergebnisse bescheren oder schädliche vermeiden. So mögen wir beispielsweise unser momentanes Verlangen nach belohnend schmackhaftem, aber fetthaltigen Essen um unserer Gesundheit im Alter Willen unterdrücken. Die Fähigkeit unsere Emotionen zu regulieren, trägt also zur Bewahrung unserer körperlichen und seelischen Gesundheit bei. Umgekehrt ist es geradezu ein charakteristisches Merkmal von Suchterkrankungen wie der Nikotinsucht, dass Süchtige unfähig sind ihr pathologisches Verlangen nach Drogen zu regulieren. Es ist daher von zentraler Bedeutung zu ermitteln, warum einige Menschen in der Lage sind, ihr Verlangen nach Belohnungen zu regulieren, andere hingegen nicht. Könnten Raucher von Emotionsregulationstrainings profitieren und lernen ihr Verlangen nach Zigaretten zu beherrschen und abstinent zu werden? In dieser Dissertation habe ich unter Zuhilfenahme der funktionellen Magnetresonanztomographie drei wichtige Fragestellungen untersucht: (a) Ist die Emotionsregulationsstrategie des Distanzierens dazu geeignet, belohnungsbezogenes Verlangen zu vermindern und neuronale Signale zu modulieren, die zur Berechnung von Belohnung beitragen? (b) Welches sind die neuronalen Prozesse, die der erfolgreichen Regulierung von Belohnungen zugrunde liegen? (c) Können Raucher Emotionsregulation dazu benutzen ihr Rauchverlangen und rauchreizbezogene Hirnaktivierungen zu mindern?

In Studie I zeige ich, dass Distanzieren bei gesunden Probanden zu einer Verminderung von Vorfreude und Freude angesichts finanzieller Belohnungen führt. Des Weiteren kann ich belegen, dass obwohl Distanzieren primär auf die Verminderung von belohnungsbezogenem Gefühlserleben abzielt, es auch zu einer Verminderung von jenen neuronalen Signalen im ventralen Striatum führt, die der Belohnungserwartung

(Erwartungswert) und der Belohnungsevaluierung (Prädiktionsfehler) zugrunde liegen. Die Ergebnisse legen Folgendes nahe: Gesunde Personen, die unliebsames Verhalten wie zum Beispiel den übermäßiger Konsum von Süßigkeiten verändern möchten, könnten Distanzieren dazu verwenden, neuronale Erwartungswertsignale von belohnungsankündigenden Hinweisreizen (wie es zum Beispiel die Ansicht eines Schoko-Riegels darstellt) zu modulieren und ihr Verlangen nach Belohnungen zu mindern. Weiterhin verdeutlichen die Effekte, dass, selbst wenn es gesunden Personen nicht gelingen sollte, der Versuchung von Belohnungen zu widerstehen, ihnen die Möglichkeit bleibt, mittels Emotionsregulation zu beeinflussen, wie viel Freude sie während des Konsums empfinden. Die Modulierung von Prädiktionsfehlern würde dann ein weiteres Hilfsmittel darstellen, mit dem Personen den Wert von Belohnungen indirekt mindern könnten.

In Studie II kann ich zeigen, dass Distanzieren von finanziellen Belohnungen nicht nur zu einer Verminderung von Vorfreude und Freude führt, sondern auch zu einer Reduktion von behavioral messbarer Motivation. Darüber hinaus belege ich, dass das Putamen eine Hirnregion ist, in der belohnungsbezogene Motivation in Handlung umgesetzt wird, und dass Distanzieren die Umwandlung von Motivation in Handlung durch eine Modulation des Putamens verhindert. Schließlich demonstriere ich, dass die erfolgreiche Beeinflussung von Erwartungswertsignalen zumindest teilweise auf eine Modulierung von Putamen Signalen seitens des DLPFC zurückzuführen ist. Die Ergebnisse zeigen also, dass Emotionsregulation neuronal und behavioral gemessene belohnungsbezogene Motivation reduziert. Dies betrachte ich als eine unabdingbare Voraussetzung, will sich Emotionsregulation als eine nützliche Strategie zur Unterbindung drogenbezogenen *Handelns* etablieren. Weiterhin erhellen die Ergebnisse die Natur präfontal-subkortikaler Interaktionen während des Regulierens von Emotionen. Bisherige Erkenntnisse über die Beteiligung des DLPFC bei der Regulierung von Amygdala Signalen im Kontext aversiver Gefühle werden auf den Geltungsbereich der Belohnungsregulation erweitert.

In Studie III schließlich kann ich belegen, dass saturierte und abstinente Raucher per Distanzieren erfolgreich ihr Rauchverlangen mindern können, wenn sie Rauchhinweisreizen in einem sicherem Laborumfeld ausgesetzt werden. Darüber hinaus finde ich, dass die Fähigkeit zur Regulierung von Rauchverlangen nicht negativ durch

die Schwere der Nikotinabhängigkeit beeinflusst wird. Im Gehirn führte Distanzieren zu einer Reduktion von Rauchhinweisreiz bezogenen Aktivierungen in Rauchstatus unabhängigen (VMPFC) als auch in Abstinenz spezifischen (Caudatus, Amygdala, subgenualer ACC) Arealen, welche mit motivationalen Aspekten von Nikotinsucht wie Rauchverlangen oder Bewertungsaspekten in Verbindung gebracht werden. Allerdings kann ich auch zeigen, dass im linken Caudatus emotionsregulationsinduzierte Signalminderungen von Rauchhinweisreizaktivierungen mit Zunahme der Nikotinabhängigkeit abnehmen. Zusammengenommen legen die Befunde von Studie III nahe, dass Raucher tatsächlich trainiert werden können, mittels Emotionsregulation ihr Rauchverlangen sowie Rauchhinweisreiz bezogene Aktivierungen in suchtrelevanten Hirnarealen herunterzuregulieren, wie es bereits in Interventionen wie dem Cue Exposure Treatment versucht wird. Zukünftige Studien müssen überprüfen, ob die Laboreffekte einer Prüfung im Feld standhalten, wo Rauchhinweisreize allgegenwärtig und Zigaretten ständig verfügbar sind. Angesichts der gängigen Theorien über eine Beteiligung des Caudatus an zielbezogener Handlungs- und Wertberechnung folgere ich weiterhin, dass temporäre Abstinenz einen Zustand bei schweren Rauchern erzeugen könnte, in dem sie nicht ohne Weiteres antrainierte Emotionsregulationsfähigkeiten benutzen können um Rauchhinweisreize zu entwerten.

List of original publications

The dissertation is based on the following original research articles:

Study I

Staudinger, M.R., Erk, S., Abler, B. & Walter, H. (2009). Cognitive reappraisal modulates expected value and prediction error encoding in the ventral striatum. *Neuroimage*. 47(2): 713-21. http://dx.doi.org/10.1016/j.neuroimage.2009.04.095

Study II

Staudinger, M.R., Erk, S. & Walter, H. (2011). Dorsolateral prefrontal cortex modulates striatal reward encoding during reappraisal of reward anticipation. *Cereb Cortex*, 21(11): 2578-88. http://dx.doi.org/10.1093/cercor/bhr041

List of abbreviations

ACC	Anterior Cingulate
ANOVA	Analysis of variance
BA	Brodmann area
BOLD	Blood oxygenation level-dependent
CR	Conditioned reinforcement
CS	Conditioned cue
DA	Dopamine
dACC	Dorsal anterior Cingulate
DLPFC	Dorsolateral prefrontal Cortex
EEG	Electroencephalography
ER	Emotion regulation
EV	Expected value
fMRI	Functional magnetic resonance imaging
FTND	Fagerström Test for Nicotine Dependence
FWE	Family-wise error rate
GABA	Gamma-aminobutyric acid
GLM	General linear model
HRF	Hemodynamic response function
IPL	Inferior parietal lobe
MEG	Magnetoencephalography
MID	Monetary incentive delay task
MNI	Montreal Neurological Institute
NACC	Nucleus accumbens
nAChR	Nicotinic acetylcholine receptor
OFC	Orbitofrontal Cortex
PE	Prediction error
PET	Positron emission tomography
PFC	Prefrontal Cortex

PIT	Pavlovian-to-instrumental transfer
PPI	Psychophysiological interaction analysis
PPM	Parts per million
RCZ	Rostral cingulate zone
RSS	Residual sum of squares
RT	Response reaction times
SCR	Skin conductance responses
SPM	Statistical parametric mapping
TDL	Temporal difference learning
TPJ	Temporal parietal junction
TR	Repetition time
VLPFC	Ventrolateral prefrontal Cortex
VMPFC	Ventromedial prefrontal Cortex
VST	Ventral striatum
VTA	Ventral tegmental area

1. Introduction

Whether we like it or not, our life is a never-ending stream of real and imagined situations that confront us with cues that indicate rewards or punishments that in turn frequently depend on the actions we take or refrain from taking. What shall we do? Often we let ourselves be influenced if not be driven by the very feelings that we anticipate our actions will produce: we decide to meet some real good friends and cook together, because we anticipate that it will feel good to eat well, to drink wine, to have stimulating conversations, and to laugh. However, the relationship between feeling and decision is not always that clear-cut. Sometimes we have to act against our own immediate feelings in order to pursue "better" actions, that is, actions that will entail delayed beneficial outcomes or avoid detrimental ones. For instance, we may resist the temptation to go shopping now in order to save money for a summer holiday trip later that year. We decide to regulate our desire for chocolate, potato chips, and spaghetti ice—be it only from time to time—for the sake of health in old age. The latter decision is particularly interesting because it requires a downregulation of positive feelings towards rewards which, at a first glance, could be regarded a foolish thing to do. However, the inability to regulate pathological desire for rewarding drugs is a central characteristic of addiction disorders such as nicotine addiction (Robinson and Berridge 2003; Everitt and Robbins 2005). It is thus imperative to determine why some people are able to regulate their desire for rewards while others are not. Furthermore, what are the cognitive regulation strategies that enable them do so? Last, could drug addicts benefit from cognitive regulation training in the regulation of drug cue-induced craving and manage to abstain? In this thesis, I will investigate whether a certain emotion regulation strategy termed distancing (Gross 2002) is suitable to attenuate emotional and motivational responses to reward cues in general and to smoking cues in nicotine addicts in particular. Furthermore, I will try to determine the neural mechanisms that underpin successful regulation of rewards. Before giving a detailed outline of the experiments, I will briefly describe the neurocircuitries of human reward processing and of nicotine addiction and introduce the concept of cognitive emotion regulation.

1.1. The human reward system

1.1.1. Functional neuroanatomy of the human reward circuitry

In 1954, Olds and Milner (Olds and Milner 1954) discovered that rats, being implanted with lever-controlled electrodes in the septal area, will stimulate themselves until exhaustion. This led to the concept of a distinct reward circuit in the brain. At the center of the animal and human reward circuit are two midbrain projection pathways: the mesolimbic and mesocortical pathways denote dopaminergic projections from the ventral tegmental area (VTA) to the ventral striatum (VST; including the nucleus accumbens [NACC]) and prefrontal cortex (PFC), respectively, whereas the nigrostriatal pathway denotes dopaminergic projections from the substantia nigra (SN) to the dorsal striatum (caudate and putamen) (Haber *et al.* 2000). For several decades, it has been assumed that mesolimbic dopamine (DA) mediates the hedonic impact attached to reward, that is, feelings of pleasure and lust. However, there is now growing evidence that basic implicit 'liking', located in NACC shell - ventral pallidal circuits, is supported by μ-opioid rather than DA neurotransmission and is only later transformed into conscious hedonic feelings in cortical areas such as the anterior cingulate and orbitofrontal cortex (Berridge 2007). Instead, DA neurotransmission supports both Pavlovian and instrumental learning. Here, DA neurons behave as if they actually obeyed predictions from classical reinforcement learning algorithms such as Temporal Difference Learning (TDL) (Sutton 1988; Schultz *et al.* 1997). During reward expectation, the DA signal conveys information about the degree to which a conditioned cue predicts the occurrence of subsequent reward, indicating the expected value (Bernoulli 1954)

$$EV = m*p \qquad (1)$$

where m and p are the magnitude and probability of the predicted reward, respectively (Schultz 2000; Knutson, Adams *et al.* 2001; O'Doherty *et al.* 2004). Upon reward receipt/omission, DA neurons seem to generate a prediction error (PE) δ by comparing the current EV to the actually received reward

$$\delta(t) = r(t) - EV(t) \qquad (2)$$

where *r(t)* is the magnitude of the received reward (Hollerman and Schultz 1998; Fiorillo *et al.* 2003; Tobler *et al.* 2005). The PE is then used to update the predictive value

$$EV(t+1) = EV(t) + \alpha * \delta(t) \qquad (3)$$

where α is the current learning rate of the organism. The striking resemblance between DA signaling and TDL predictions led researchers to conclude that DA transmission serves as a teaching signal that drives agents to adapt their behavior to be able to maximize future reward receipt (Montague *et al.* 2004). However, Berridge and Robinson argue that besides formal predictive value, learning within the mesolimbic VTA – NACC system, via Pavlovian stimulus-stimulus associations, also assigns 'incentive salience' to predictive cues. This renders the cue and its associated reward 'wanted' targets of motivated behavior (Berridge and Robinson 2003; Berridge 2007). Incentive salience may be best understood as an implicit form of motivation that influences behavior without the person necessarily experiencing conscious feelings (Winkielman *et al.* 2005); it can be transformed into explicit desire via cognitive valuation in prefrontal areas though (Berridge and Robinson 2003).

Although PE responses can be found throughout the human striatum (McClure *et al.* 2003; O'Doherty, Dayan *et al.* 2003; Preuschoff *et al.* 2006; Schonberg *et al.* 2007) and midbrain (Murray *et al.* 2007; D'Ardenne *et al.* 2008), substantial local functional dissociations have been revealed. Using both Pavlovian and instrumental conditioning procedures and fMRI, O'Doherty and colleagues showed that the VST is activated during both forms of learning, whereas the caudate is involved in instrumental learning exclusively (O'Doherty *et al.* 2004). This finding concurs with the notion that instrumental learning is implemented via two distinct modules (Sutton and Barto 1988): the 'critic' learns to predict future reward by shaping up cue-reward associations (stimulus-outcome mappings), regardless of whether the agent acted or not. The 'actor', however, specifically monitors whether actions of the agent led to rewards and learns to

choose the most successful actions, thus shaping up policies or stimulus-response-outcome mappings. Besides differential contributions of the VST versus caudate to the critic and actor (Haruno *et al.* 2004; Tricomi *et al.* 2004; Schonberg *et al.* 2007), another functional dissociation has been established. The putamen is implicated in action preparation and initiation (Jaeger *et al.* 1993; Boussaoud and Kermadi 1997; Krams *et al.* 1998). More precisely, it facilitates and suppresses execution of particular actions via projections to the direct and indirect pathway, respectively (Frank *et al.* 2004; Aron *et al.* 2009). In contrast to the critic and actor, the putamen is not outcome-sensitive per se but contributes to the programming of habitual, stimulus driven motor behavior, irrespective of whether actions are rewarded or not (stimulus-response mappings) (Yin *et al.* 2004; Yin and Knowlton 2006; Tricomi *et al.* 2009).

1.1.2. Cortico-basal ganglia loops

The functional segregation of the striatum was further corroborated by the discovery of separated, parallel operating cortical-basal ganglia-thalamo-cortical loops (Alexander *et al.* 1990): first, the affective loop, connecting the ventromedial PFC (VMPFC), orbitofrontal cortex (OFC), and dorsal anterior cingulate (dACC) to the VST, with the VMPFC occupying the most medial terminal fields (NACC), the dACC projecting more dorsolateral, and the OFC terminating in between (Haber *et al.* 2006; Haber and Knutson 2010); second, the associative loop, connecting the dorsolateral PFC (DLPFC) to the caudate; third, the sensorimotor loop, connecting the premotor cortex and supplementary motor area (SMA) to the putamen (loop 4 and 5 omitted for brevity). Each striatal region projects back to the originating cortical region via distinct pallidal and thalamic relays (Alexander *et al.* 1990; Aron *et al.* 2009). The functions of the sensorimotor loop correspond to those of the putamen, that is, on a short time scale, the facilitation and suppression of motor plans, on a long time scale, the formation of habits (Yin and Knowlton 2006; Balleine and O'Doherty 2010). The affective loop is implicated in anticipation and valuation of rewards, ranging from primary (e.g., food, sweet tastes) (O'Doherty, Dayan *et al.* 2003; Beaver *et al.* 2006) to secondary (e.g., money, attractive faces) rewards (Aharon *et al.* 2001; Knutson *et al.* 2005). Furthermore, recent evidence points to a role for the VMPFC subcomponent in the

representation of decision values (e.g., willingness-to-pay) for various rewarding goods (Plassmann *et al.* 2007; Chib *et al.* 2009) as well as of goal values of chosen actions (Wunderlich *et al.* 2009). Unlike the VST, which predicts reward in the presence of Pavlovian cues, the VMPFC encodes values of actions independent of discriminative cues (Valentin *et al.* 2007; Glascher *et al.* 2009). It does so by determining the reward value of the subsequent outcome on the basis of consummatory experience (Balleine and O'Doherty 2010). The action-outcome sensitivity of both the VMPFC and the caudate led to the idea of an additional circuit that links the VMPFC and caudate and mediates goal-directed action selection and learning (Balleine and O'Doherty 2010). Finally, the DLPFC is involved in diverse executive control subfunctions such as working memory (Smith and Jonides 1997), planning (Grahn *et al.* 2008), and rule-based action selection (Jiang and Kanwisher 2003), suggesting that the DLPFC links short-term memory information to goal-directed action (Ridderinkhof, van den Wildenberg *et al.* 2004). Furthermore, the DLPFC (Brodmann areas [BA] 9 and 46) plays a key role in human self-control, for instance, choices of later-larger over sooner-smaller rewards (Figner *et al.* 2010), the rejection of risky options (Knoch *et al.* 2006), or dieters' decisions to not eat liked-but-unhealthy food (Hare *et al.* 2009). Therefore, the associative loop may represent a pathway by which executive control modulates goal values in the caudate and VMPFC (Haber *et al.* 2006; Grahn *et al.* 2008; Hare *et al.* 2009) and thus align goal-directed action selection with long-term beneficial goals.

If the affective network motivated, the associative network planned, and the sensorimotor network executed action (Grahn *et al.* 2008), how would these different aspects of reward-related action come together to form complex goal-directed behavior? The past decade saw the emergence of novel answers to the old question of 'how motivation translates into action' (Mogenson *et al.* 1980). For certain innate, unconditioned, or subliminal actions (e.g., feeding, drinking), the VST may trigger motivated behavior directly via ventral pallidal and nigral relays (Mogenson *et al.* 1980; Groenewegen and Trimble 2007; Pessiglione *et al.* 2007). In the case of complex motor behavior, the VST (representing Pavlovian values) could facilitate action via so-called striato-nigro-striatal spiral loops (Haber *et al.* 2000; Groenewegen and Trimble 2007), which transfer Pavlovian information to ever more dorsal and lateral striatal regions and thus increase the vigor of goal-directed (caudate) action or habitual (putamen) action

(Balleine and O'Doherty 2010). Indirect evidence for propagation of reward-related information came from a human fMRI study that showed that reward PE appeared first within the VMPFC-VST circuit and only 2-4s later in the caudate and putamen (Haber and Knutson 2010). Alternatively, integration of affective, associative and sensorimotor information could be accomplished in convergence zones, where diffuse PFC projections from different loops converge onto common striatal, pallidal, and nigral targets and thus permit information exchange among the circuits (Joel and Weiner 1994; Haber *et al.* 2006; Draganski *et al.* 2008; Balleine and O'Doherty 2010).

1.2. Nicotine addiction

Every year, 110.000 to 140.000 German people die due to the consequences of smoking, mostly because of cancer or cardiovascular diseases (Batra and Buchkremer 2003). The adult 30-day prevalence of becoming nicotine addicted is approximately 35% (Kraus and Augustin 2001). One in every third smoker attempts to quit smoking at least once per year (Bundesgesundheitssurvey 1999). In face of such grim statistics, it is imperative to find suitable self-management strategies that help smokers quit smoking and prevent relapse.

1.2.1. Functional neuroanatomy of nicotine addiction with an emphasis on drug-conditioned cues

Nicotine is the primary addictive component of tobacco smoke (Balfour 2004). It is widely accepted that nicotine unfolds its effects mainly through excitation of the mesolimbic and, to a lesser extent, nigrostriatal, pathways (Di Chiara and Imperato 1988; Corrigall *et al.* 1994; Keath *et al.* 2007). Precisely, nicotine stimulates nicotinic acetylcholine receptors (nAChRs) on DA neurons in the VTA (Mansvelder *et al.* 2002), entailing DA neuron burst firing (Balfour *et al.* 2000) and extracellular DA overflow in the shell (Imperato *et al.* 1986) and, after pretreatment, core of the NACC (Cadoni and Di Chiara 2000). After the rapid desensitization of these nAChRs, sustained excitation of the mesolimbic pathway is caused by both depression of inhibitory GABAergic and enhancement of excitatory glutamatergic input on DA neurons (Mansvelder *et al.* 2002; Laviolette and van der Kooy 2004). Paradoxically, the magnitude of nicotine-induced

DA overflow in the NACC is small when compared to the ones seen with other addictive drugs (e.g., amphetamine or cocaine) (Balfour 2004). Furthermore, on first contact, nicotine can produce potent aversive side-effects such as anxiety, nausea, and dizziness (Laviolette and van der Kooy 2004). Hence, the immediate hedonic effects of nicotine consumption, on their own, are unlikely to explain the development of dependence. Consequently, the focus has shifted to the investigation of the role of drug-associated stimuli (conditioned cues, CS) in the development and maintenance of addiction (Niaura *et al.* 1988). Environmental stimuli such as cigarettes, cigarette packs, bars, parties, or smoking subjects, through repeated pairing with the acute rewarding effects of nicotine (Pavlovian conditioning), acquire incentive properties themselves and become so-called conditioned reinforcers (Di Chiara 2002). According to the incentive-sensitization theory (Robinson and Berridge 2003; Berridge 2007), compulsive drug pursuit is primarily a consequence of aberrant incentive salience attribution to CS, caused by sensitization of the mesolimbic pathway. Sensitization, as opposed to tolerance, refers to the phenomenon that some drug effects increase over time. Repeated drug exposure has been shown to progressively increase psychomotor stimulant responses such as locomotion, exploration and speech, an effect termed behavioral sensitization (Strakowski *et al.* 1996). Behavioral sensitization is at least partly caused by the drug's ability to increase DA efflux, to induce hypersensitivity of DA receptors, and to alter DA receptor gene expression in the NACC shell with repeated drug exposure (Kalivas and Stewart 1991; Parkinson *et al.* 1999; Nestler 2001; Di Chiara 2002; Le Foll *et al.* 2003; Robinson and Berridge 2003). Robinson and Berridge argue that these alterations give rise to a second effect, namely, the sensitization of incentive motivation. Because mesolimbic DA assigns incentive salience to predictive cues, drug-induced sensitization of the mesolimbic pathway entails excessive incentive attribution to drug CS, causing pathological implicit and, after cognitive, prefrontal elaboration, explicit wanting for the drug (craving) (Robinson and Berridge 2003).

Learned conditioned reinforcers may contribute to drug-seeking in different ways: first, they can initiate Pavlovian approach, that is, relatively automatic and reflexive approach and consummatory behavior (Day *et al.* 2006). Second, when drugs are delivered only after numerous instrumental responses (during so called 2nd order schedules), response-dependent presentations of conditioned reinforcers sustain

instrumental responding. This response-enhancing effect is called conditioned reinforcement (CR) (Kelleher 1966; Everitt and Robbins 2000). Hence, conditioned reinforcers can maintain drug-seeking when nicotine is not immediately available, bridging the gap until drug receipt (Cohen *et al.* 2004; Everitt and Robbins 2005). Third, conditioned reinforcers even facilitate the learning of completely new drug-seeking responses that can persist for months (Di Ciano and Everitt 2004). Fourth, when presented response-independently, CS can increase the frequency of instrumental drug-responding considerably, an effect termed Pavlovian-to-instrumental transfer (PIT) (Bower and Grusec 1964). Thus, another mechanism by which CS contribute to drug-seeking is by invigorating drug-seeking behavior itself (Everitt and Robbins 2005). There is some unresolved controversy about the striatal regions that support CS enhancement of drug seeking. Some studies reported that CR and PIT depended on the integrity of the NACC core (Parkinson *et al.* 1999; Hall *et al.* 2001), whereas others found the NACC shell to be causally involved in Pavlovian conditioning and PIT (Corbit *et al.* 2001; Di Chiara 2002). In human functional magnetic resonance imaging (fMRI) studies, enhanced PIT-related blood oxygenation level-dependent (BOLD) activity was observed in the NACC and in the ventrolateral putamen (Bray *et al.* 2008; Talmi *et al.* 2008).

In sum, the evidence points to a role for the shell in the direct psychomotor (DA-mediated) and hedonic (opiate-mediated) drug effects as well as for the core in the implementation of CS influence over instrumental behavior (DA-mediated). Finally, the response-enhancing and motivation-inducing qualities of conditioned reinforcers may explain why smoking CS, like stress and drug injections, have the powerful ability to trigger craving and to reinstate drug-seeking behavior after prolonged periods of abstinence (Niaura *et al.* 1988; Shaham *et al.* 2003; Tong *et al.* 2007; Ferguson and Shiffman 2009; Janes *et al.* 2010). In fact, this ability might even increase with duration of abstinence (Lu *et al.* 2004). The involvement of drug CS in the maintenance of and relapse to drug taking has given rise to alternative treatment strategies such as the cue exposure approach (Drummond *et al.* 1995). In cue exposure treatment, addicts are exposed to drug CS to provoke cue reactivity, that is, conditioned responses to drug CS such as craving. The idea behind cue exposure treatment is that (a) repeated exposure to drug CS without reinforcement will extinguish the conditioned responses to drug CS

and (b) addicts are given the opportunity to rehearse trained coping strategies in a safe environment (Drummond *et al.* 1995; Drummond 2001; Barlow *et al.* 2004).

The incentive-sensitization theory view posits that compulsive drug pursuit is mainly caused by CS-elicited pathological wanting. By contrast, according to the habit view (Everitt and Robbins 2005), compulsive drug pursuit is primarily initiated by CS-elicited habits. Everitt and Robbins argue that initial drug use can be characterized as voluntary and goal-directed in that drug users experience rewarding and hedonic drug effects. However, a central characteristic of the transition to compulsive drug taking and thus dependence is that it may take place in the absence of any pleasurable feelings. In this state, drug seeking and taking is no longer controlled by goals but by persistent, invariable stimulus-response patterns, that is, habits. On closer inspection, both theories make very similar assumptions about the quality of the subjective experience on CS contact ('wanting' versus 'must do!') (Everitt and Robbins 2005). On the neural level, however, they differ considerably. Whereas the incentive-sensitization view locates the origin of compulsive drug seeking in the VST (NACC), the habit view predicts that the progression from voluntary to compulsive drug use is reflected in a shift from prefrontal to striatal as well as in a transfer from ventral to dorsal striatal control over behavior (Everitt and Robbins 2005), the latter presumably mediated by the striato-nigro-striatal spiral loops (Belin and Everitt 2008). This hypothesis is mainly motivated by findings from cocaine addiction research: animal (Ito *et al.* 2000; Ito *et al.* 2002) and human imaging (Garavan *et al.* 2000; Volkow *et al.* 2006; Wong *et al.* 2006) studies have reported cocaine CS- or cocaine craving-related activation of the dorsal striatum, and infusions of DA antagonists into the dorsal striatum greatly decrease cocaine seeking behavior (Vanderschuren *et al.* 2005; Belin and Everitt 2008). Furthermore, an 'inner-striatal' shift might also occur during the transfer from light to heavy alcohol drinking (Grüsser *et al.* 2004; Vollstädt-Klein *et al.* 2010). In the case of nicotine addiction, however, the empirical evidence is not that conclusive: while several fMRI studies in humans observed that smoking CS-induced activity was restricted to the dorsal striatum (Janse Van Rensburg *et al.* 2008; McClernon *et al.* 2008; Janes *et al.* 2010), others did report activations in the NACC or VTA (Due *et al.* 2002; David *et al.* 2005; Smolka *et al.* 2006; David 2007; Franklin *et al.* 2007; Wang *et al.* 2007; Stippekohl *et al.* 2010). Another fMRI study (McClernon *et al.* 2007) found smoking CS-induced activity in the

dorsal striatum correlated positively with a behavioral measure for nicotine dependence, the Fagerström Test for Nicotine Dependence (FTND) score (Heatherton *et al.* 1991), thereby lending indirect support to a putative ventral-to-dorsal transition.

1.2.2. Deficient self-control/ altered impulsivity in smokers

It has been hypothesized that long-time drug taking induces neuroplastic changes within the PFC (Volkow *et al.* 1991; Liu *et al.* 1998; Jentsch and Taylor 1999; Tabibnia *et al.* 2011) and that these changes cause diminished activity in prefrontal regions that are involved in self-control (Goldstein and Volkow 2002; Volkow *et al.* 2004). As a consequence, addicts may acquire an inability to inhibit the strong motivational and habitual impulses that are triggered by drug CS. This may additionally amplify the compulsive drug pursuit (Jentsch and Taylor 1999; Robinson and Berridge 2003; Bechara 2005; Everitt and Robbins 2005). Self-control can be understood as the ability to inhibit actions, thoughts, or feelings that are either not relevant to the task at hand or are not desirable/detrimental (Muraven and Baumeister 2000; Cohen and Lieberman 2010). Although one can distinguish between motor, cognitive, and affective inhibitory control, these different kinds of self-control share a common neural substrate (Muraven and Baumeister 2000; Cohen and Lieberman 2010; Tabibnia *et al.* 2011). Indeed, chronic exposure to some drugs (e.g., cocaine, amphetamine) has been shown to decrease gray matter volumes (Liu *et al.* 1998; Tabibnia *et al.* 2011) and to alter DA transmission within the PFC (Volkow *et al.* 1991; Jentsch and Taylor 1999), resulting in diminished activity in frontal regions involved in self-control (ACC, DLPFC) and decision making (OFC) (Goldstein and Volkow 2002; Volkow *et al.* 2004). Thus, long-time drug taking seems to induce neuroplastic changes within the PFC that disrupt inhibitory top-down control over drug seeking behavior. What is more, these changes may also compromise prefrontal functioning in non-drug contexts: cocaine and amphetamine users, alcoholics as well as pathological gamblers, show marked deficits in a variety of cognitive control tasks that explore PFC functioning such as the Wisconsin card sorting test (Bechara *et al.* 2001), the gambling task (Bechara *et al.* 2001), the reversal learning paradigm (de Ruiter *et al.* 2009), the Go/Nogo task (Monterosso *et al.* 2005; Noël *et al.* 2005; Tabibnia *et al.* 2011), and in affect regulation

paradigms (Tabibnia *et al.* 2011). By contrast, although nicotine seems to affect gray matter densities and volumes in the DLPFC, ACC, and OFC (Brody *et al.* 2004; Kühn *et al.* 2010), evidence for comparable neuropsychological deficits in smokers is lacking (de Ruiter *et al.* 2009). However, nicotine addiction is associated with impulsivity, a personality trait that refers to the tendency to act prematurely without forethought as to the consequences of actions (Durana and Barnes 1993). Impulsivity is a multifaceted construct that can manifest itself in preferences for immediate gratification (impulsive choice) as well as in risky activities, novel seeking, failure of motor inhibition (impulsive action), or diminished persistence during a task at hand (McCown *et al.* 1993; Dalley *et al.* 2011). Compared to control participants, smokers exhibit higher trait impulsivity scores as measured by personality questionnaires like Barratt's Impulsivity Scale or the Sensation-Seeking Scale (Mitchell 1999). Furthermore, they show steeper money delay discounting than controls, that is, an increased preference of small, immediate over large, delayed reward, indicative of impulsive choice behavior (Bickel *et al.* 1999; Mitchell 1999; Johnson *et al.* 2007; Bickel *et al.* 2008; Businelle *et al.* 2011; Peters *et al.* 2011; Peters and Büchel 2011). This is accompanied by blunted responses to delayed reward in the VST (Luo *et al.* 2011). Smokers discount cigarettes even more than money (Bickel *et al.* 1999; Field *et al.* 2006; Johnson *et al.* 2007).

Thus, the association of nicotine addiction and impulsivity is suggestive of self-control deficiencies within and beyond the drug domain. However, a longitudinal studies in a cohort of adolescents demonstrated that money delay discounting promotes smoking (Audrain-McGovern *et al.* 2009) and not vice versa. Hence, impulsivity itself might preexist as a personality trait in smokers. Such a view concurs with the finding that preselected high-impulsive rats show enhanced rates of nicotine self-administration and higher vulnerability to relapse compared with low-impulsive rats (Diergaarde *et al.* 2008). The neural mechanisms that cause impulsivity in the first place, however, remain unclear. While some theories posit that the premorbid reward system is under-responsive to non-drug rewards (Blum *et al.* 2000), others argue the converse (Newman and Wallace 1993). In fact, both hypo- and hypersensitivity could lead to an increased pursuit of immediate gratification and to a susceptibility to nicotine's immediate rewarding effects.

In sum, nicotine seems to affect self- and cognitive control functions to a lesser extent than more potent drugs do. Premorbid impulsivity, along with an altered striatal sensitivity to non-drug rewards (Peters *et al.* 2011), may predispose for the development of later nicotine addiction. Impulsive striatal signals representing cue-triggered wanting *and*, in later phases, habits could override prefrontal inhibitory control attempts and entail a loss of willpower to resist smoking (Bechara 2005).

1.3. Cognitive emotion regulation

1.3.1. Emotions

To understand the concept of emotion regulation, it is first necessary to define what it is that is going to be regulated. There is consensus (Scherer 1984; Diener 1999) that emotions arise as responses to external stimuli or to internal mental representations that may encompass changes along the following distinct dimensions: 1) subjective experience 2) behavioral expression (e.g., mimic, gesture) 3) central or peripheral physiology (e.g., heart rate, blood pressure, skin conductance, hormone secretion) 4) cognitive appraisal and 5) motivation. The experiential component is the equivalent of what people describe in everyday usage as 'feeling', that is, how it feels like for an individual to experience basic emotions such as anger, fear, sadness, love, joy, or surprise. The appraisal component in turn refers to the phenomenon that such subjective feelings do not necessarily match the objective properties of the triggering stimulus. Rather, subjective feelings are mediated by the individual's *interpretations* of the stimulus. Consequently, one and the same stimulus may entail different emotional reactions due to differential interpretations. In their classic experiment, Schachter and Singer (Schachter and Singer 1962) showed that subjects who have no immediate explanations for increases in their physiological arousal (due to epinephrine injections and non- or misinformation about its side effects) will label their subjective feelings in accordance with appraisals provided by the environment. If an alleged co-participant, in reality a stooge of the experimenters, displayed anger during a waiting period, the subjects reported that they had felt anger too. By contrast, if the stooge showed signs of euphoria, the subjects felt euphoric. This experiment for the first time provided evidence

that cognitive judgments can tremendously alter emotional experience. Cognitive appraisals can be understood as individual assessments of the stimulus along several central dimensions such as novelty, valence (pleasantness/unpleasantness), predictability of events to follow, sense of agency, compatibility with social or personal norms, and relevance for individual goals (Ellsworth and Scherer 2003). Such goals may be conscious (winning a game) or unconscious (avoiding an obstacle). Furthermore, they can be central (being a good father) or peripheral (being a hearty eater) to the individual's self-esteem (Gross and Thompson 2007). Whatever the affected goal, emotions are able to elicit response tendencies, for instance, the tendency to flee at the sight of a snake, or the drive to embrace a good friend (Frijda 1987), and thus change motivation. In contrast to reflexes or fixed action patterns, however, emotions allow flexibility of motivated actions (Ellsworth and Scherer 2003). One and the same stimulus may entail different behavioral responses, because the individual either reappraises the stimulus itself (e.g., realizing that the snake really is a blindworm) or considers response alternatives (e.g., freezing, because rapid movements cause snakes to bite). This flexibility of emotions constitute a great advantage for adaptive functioning (Ellsworth and Scherer 2003; Ochsner and Gross 2005). Furthermore, the fact that cognitive (re)appraisals can modify all the other components of emotions (subjective experience, behavioral expression, physiology, and motivation) renders them a particularly suitable target for emotion regulation interventions (Gross and Thompson 2007).

1.3.2. Emotion regulation

To work successfully, to relate to others in a satisfying way, or to have a rich inner life, we have to be able to produce and express positive emotions as well as to modulate negative ones. Moreover, the ability to perceive and identify emotions in oneself *and others*—termed emotional intelligence—is a personality trait that enhances personal growth and social relations (Mayer *et al.* 2000). Consequently, emotion regulation (ER) is an essential means to preserve mental health (Gross 1995). Indeed, deficient regulation of negative emotions contributes to a variety of psychiatric conditions such as major depression, nicotine addiction, anxiety disorders, impulse control disorders, or

personality disorders (e.g., Antisocial or Borderline personality disorder) (Linehan 1993; Davidson *et al.* 2000; Davidson *et al.* 2002; Johnson *et al.* 2003; Campbell-Sills and Barlow 2007; Fucito *et al.* 2010). By contrast, greater everyday life use of ER (i.e., reappraisal, see below) is associated with higher overall levels of positive as well as lower levels of negative affect, better interpersonal functioning, and greater psychological well-being (Gross and John 2003). In fMRI experiments, depressed individuals demonstrate diminished recruitment of the PFC during the regulation of negative feelings, resulting in increases of amygdala activity and negative affect (Beauregard *et al.* 2006; Johnstone *et al.* 2007; Erk *et al.* 2010). Conversely, everyday reappraisers show increased recruitment of prefrontal areas and decreased amygdala activity during the processing of negative facial expressions (Drabant *et al.* 2009). In sum, it seems that habitual emotion regulation is already an integral characteristic of psychological functioning. But what is ER?

According to Gross' definition (Gross 1998b), ER refers "to the processes by which we influence which emotions we have, when we have them, and how we experience and express them". Such a deliberate act of processing and expressing emotions also underlies the concept of emotional approach coping (Stanton *et al.* 1994) ER strategies themselves have been divided into antecedent-focused and response-focused approaches (Gross 2002). While antecedent-focused ER aims at modifying the external or internal environment before the emotional responses (subjective experience, expression, physiology) have fully unfold, response-focused ER manipulate these very responses once they are present. Four different types of antecedent-focused ER are distinguished (Gross 1998b; Gross 2002): the first, situation selection, refers to the fact that we can decide which situations, that is, places, people, or events, to approach or to avoid in order to have or not have particular emotions. We may avoid going to the dentist for years because we are afraid of the pain we might experience. We may also decide to go out and party frequently because we anticipate the joy of meeting a woman. Second, once a situation has been selected, it can be modified in order to change the impact it has on us (situation modification). For instance, confronted with an unavoidable lecture, we could decide not to go for the conventional chalk-and-talk but to engage the students in permanent lively discussions if we felt uncomfortable being the center of attention. Third, as most given situations have several different aspects, we

can choose which aspects we want to pay attention to (attentional deployment). Sitting in the dentist's chair, we may decide to focus on calming our breathing rather then to focus on the drill so as to be able to relax. Fourth, particular aspects of situations do not have fixed meanings. That means that for any given aspect of a situation we focus on, we have the freedom to decide which of the possible meanings we would like to assign. We can attribute our failing a test to external rather than internal factors. We may also attribute a colleague's not greeting us to his momentary sulkiness rather than to conclude that he does not like us. This capacity to cognitively change meanings of situations (aspects, stimuli) is termed reappraisal. Last, unlike the ER strategies already mentioned, there is a fifth ER strategy termed response modulation that does not act on emotion antecedents but on already-elicited emotional responses. During one such response modulation strategy, termed suppression, the individual simply tries to inhibit the behavioral expression (mimic, gesture) of a feeling. For instance, one could show a neutral face despite being very angry,. The individual might also address the feeling itself, for example, by suppressing a growing fear. Finally, medical aids (e.g., benzodiazepine, valerian) or activities (exercise, relaxation) are often used to decrease both the experiential and physiological components of certain elicited emotions (e.g., fear, sadness).

Although Gross (Gross 1998b; Gross 2002) originally drew a clear line between antecedent-focused and response-focused ER strategies, it is evident that in reality such a rigid distinction does not hold. First, emotions are not a dead end, meaning that antecedent-focused ER strategies can also be used to modify *existing* emotional responses: fear-eliciting situations can be fled (situation selection), fears can greatly diminish when being communicated (situation modification) or when one tries not to worry about the fear-accompanying arousal (attentional deployment), and fear may even be interpreted as an aid to sharpen our senses and to enhance mindfulness (cognitive change). Thus, to cover the complexity of human emotion-related behavior it may be better to think in terms of emotion cycles (Gross and Thompson 2007): situations call for ER efforts that trigger specific emotions that in turn alter original situations, receive social feedback, and are subjected to new ER so that the emotion generative process begins anew (imagine a boy who regulates his fear, asks out an adored girl, receives positive feedback, feels relief, turns relief into euphoria, etc.). Furthermore, in order to

manage highly emotional events individuals often do not rely on one single ER strategy but deploy multiple ER methods at a time.

When one thinks in terms of successful regulation of emotion subcomponents, are some ER strategies more promising than others? In a review paper (Gross 2002), Gross summarized findings from previous studies that enabled him to compare two ER strategies, reappraisal and suppression, regarding their effects on emotion experience, behavioral expression, physiological arousal, memory performance, and social feedback. The analyses showed that, when the intention lies in the downregulation of feelings, reappraisal is clearly superior to suppression. Reappraisal decreases emotion experience and emotion-expressive behavior without detrimental effects on physiological arousal or memory for information that was presented during the ER period. By contrast, although suppression inhibits emotion-expressive behavior and diminishes positive feelings, it does not decrease negative emotion experience. What is more, compared to reappraisal, suppression impacts suppressers' memory, leads to significant increases in sympathetic activation (e.g., blood pressure) in suppressers *and* their social partners, and entails lower likeability ratings of suppressers as well as weakened social support.

Of the numerous reappraisal strategies, the so-called distancing strategy has received particular attention. Distancing implements the concept of reappraisal in that the individual tries to construe the "potentially emotion-eliciting situation in non-emotional terms" (Gross 2002). The central idea of distancing is to maintain a cognitive state in which the subject detaches itself from all potentially upcoming feelings and behaves as if it was a neutral observer. Under laboratory conditions, distancing has proven very effective in reducing negative (Gross 2002; Ochsner *et al.* 2002; Kalisch *et al.* 2005; Eippert *et al.* 2007; Walter *et al.* 2009; Koenigsberg *et al.* 2010; Schardt *et al.* 2010) and positive affect (Kim and Hamann 2007) as well as sexual lust (Beauregard *et al.* 2001) in healthy participants and, to some extent, in depressed (Erk *et al.* 2010) and Borderline patients (Koenigsberg *et al.* 2009). Like other reappraisal strategies, it has been shown to induce fMRI activation in parietal and frontal areas such as the inferior parietal lobe, the DLPFC, the dACC, and the OFC (Beauregard *et al.* 2001; Kalisch *et al.* 2005; Urry *et al.* 2006; Eippert *et al.* 2007; Johnstone *et al.* 2007; Kim and Hamann 2007; Walter *et al.* 2009; Erk *et al.* 2010; Schardt *et al.* 2010). At the same time,

amygdala fMRI responses to negative (Ochsner *et al.* 2004; Eippert *et al.* 2007; Walter *et al.* 2009; Erk *et al.* 2010; Schardt *et al.* 2010) and positive pictures (Kim and Hamann 2007), to aversive social cues (Koenigsberg *et al.* 2010) as well as to erotic stimuli (Beauregard *et al.* 2001) decrease, which led to the speculation that cortical ER areas inhibit subcortical stimulus responsivity. Few studies have addressed this issue properly by using more sophisticated analysis techniques. In 2008, Wager and colleagues (Wager *et al.* 2008) showed that right ventrolateral PFC (VLPFC) fMRI activity during reappraisal of negative pictures correlated with self-reported reduction of negative emotion experience. Using pathway mapping analysis, the authors then identified two separable subcortical pathways that mediated the VLPFC influence on reappraisal success. While the first path through the NACC predicted reduced negative emotion experience, the second path through the amygdala surprisingly predicted *increased* negative emotion experience. This finding speaks against a particular involvement of the VLPFC in the direct inhibition of the amygdala. By contrast, studies on distancing from negative picture content (Erk *et al.* 2010; Schardt *et al.* 2010) that deployed psychophysiological interaction analyses (Friston *et al.* 1997) demonstrated that diminished amygdala fMRI responses could actually be a result of increased coupling of the DLPFC, dACC, and VMPFC to the amygdala during distancing.

2. Research questions and hypotheses

ER effectively attenuates negative feelings. This raises the question whether ER might be a suitable self-management strategy for smokers, that is, whether ER could help smokers to decrease their craving for smoking and in so doing support smoking cessation attempts. Of all the ER strategies discussed so far, distancing is certainly the most promising one for several reasons: first, situation selection is not an appropriate strategy, as it is almost impossible for smokers to avoid smoking cues and smoking environments, unless they are willing to live a very solitary and unsociable life. Second, smoking environments such as bars, parties, or concerts are not that easily modified (imagine yourself trying to bar a party crowd from smoking), and smoking cues cannot easily be ignored via attentional distraction. Hence, it may be wise for smokers to accept that they are going to be confronted with smoking cues to the end of their lives. Upon cue contact, suppression of craving is not advisable, because suppression increases physiological arousal and thus promotes stress which in turn increases the likelihood of relapse (Gross 2002). Because craving itself denotes already a state of heightened mental and bodily tension, relaxation should be a primary goal of craving reduction strategies. Distancing aims directly at such relaxation, and could reduce craving for smoking before and even after it has unfold.

In chapter 1.2.1, I have described how conditioned smoking cues trigger craving, that craving for smoking can be understood as a pathologically form of wanting, and that the capacity of smoking cues to elicit craving is to a good part linked to their ability to induce aberrant responses in the brain reward system. To answer the question of whether distancing may decrease craving, it would be a good starting point to ask whether distancing may reduce *reward-related* feelings and corresponding brain signals *at all*. Therefore, a stepwise approach would imply that I first demonstrated that healthy participants are able to attenuate their desire for non-drug rewards using distancing and that such reductions in emotion experience are accompanied by fMRI signal decreases in reward processing areas. In principle, ER regions could modulate striatal reward signals via cortico-basal ganglia projections (chapter 1.1.2). If I successfully

demonstrated such an interaction between distancing and reward in healthy participants, I could move on and investigate in a sample of smokers whether distancing also reduced craving for smoking and smoking cue-related brain activations.

Note that at the time of the start of my experiments in 2006, those were completely new and unanswered research questions. In the meantime, some progress has been made parallel to my investigations. Delgado and colleagues (Delgado *et al.* 2008) instructed participants to conjure calming nature sceneries while they viewed cues that predicted monetary reward. Such disengagement from reward information led to a decrease in self-reported excitement to win money. It also attenuated both cue-related fMRI activity in the striatum (caudate) and physiological arousal as indicated by skin conductance responses (SCR). The experiment thus proved for the first time that ER can modulate reward expectation at the level of emotion experience, peripheral physiology, and neural encoding. Notably, ER-related increases in DLPFC activity were positively correlated with successful regulation of SCR and negatively correlated with striatal cue responsivity. In 2009, Wang et al. (Wang *et al.* 2009) reported that suppression of hunger during the presentation of favorite food items results in reduction of positron emission tomography (PET) activation of the OFC, putamen, insula, hippocampus, and amygdala. Unfortunately, this effect was restricted to male participants. In 2010, ER was for the first time investigated with regard to its suitability to reduce drug craving. Volkow and colleagues (Volkow *et al.* 2010) instructed cocaine abusers who watched cocaine cue videos either to suppress or to permit craving. Permitting craving increased self-reported post- versus pre-video craving ratings, whereas suppression entailed no such craving change. At the neural level, cognitive inhibition reduced brain glucose metabolism as measured by 2-deoxy-2[18F]-fluoro-D-glucose PET in the OFC and NACC compared to both baseline measurements (no video) and permitting craving. Like in the Delgado experiment, reduction of striatal cue responses correlated negatively with metabolic ER-related increases in the PFC, this time the VLPFC (BA 44). Unfortunately, suppression was not successful in preventing increases in heart rate and blood pressure, limiting conclusions about its usefulness in real-life interventions. Finally, Kober and colleagues (Kober *et al.* 2010) published a study that investigated the cognitive regulation of craving for cigarettes and for food in current smokers: participants were presented with cigarette- and food-associated cues while applying

either of the following cognitive strategies: for the control strategy, participants were instructed to think about the immediate feelings associated with smoking or eating. For the regulate strategy, participants were asked to think about the long-term detrimental effects of smoking and eating high-caloric food. Such negative reappraisal significantly reduced cravings for both smoking and food. Furthermore, it attenuated fMRI activity in the VST, VTA, subgenual ACC, and amygdala and increased activity in previously reported ER-associated areas such as the DLPFC, VLPFC, and dorsomedial PFC. Importantly, both decreases in the VST and increases in the DLPFC correlated with self-reported craving reduction. Moreover, the inverse relationship between DLPFC activity and craving was mediated by activation reductions in the VST, suggesting that craving reductions were attributable to top-down inhibition of the VST by the DLPFC.

2.1 Distancing from monetary reward in healthy participants

In the introduction, I have shown that distancing reduces negative emotion experience and amygdala signals in participants who are watching emotion-eliciting pictures. The aim of the first experiment now was to investigate whether distancing also reduces reward-related feelings. Furthermore, I aimed to determine whether successful attenuation of positive emotion experience was accompanied by signals reductions in the VST. As monetary rewards reliably activate the VST (Knutson, Adams *et al.* 2001; Knutson, Fong *et al.* 2001; Abler *et al.* 2005; Knutson *et al.* 2005; Abler *et al.* 2006), I used fMRI and a modified version of the monetary incentive delay task (MID) (Knutson, Adams *et al.* 2001). The MID allows investigation of striatal reward signals in two distinct phases: EV signals during reward anticipation and PE signals upon reward receipt/omission (see chapter 1.1).

I expected that distancing

(I) elicits activity in brain regions reportedly implicated in distancing such as the DLPFC, dACC, and OFC

(II) attenuates overall levels of positive affect (as indicated by a joint measure of eager anticipation of and pleasure upon winning monetary reward)

(III) attenuates EV and PE encoding in the VST

2.2 Connectivity changes during the regulation of reward motivation in healthy participants

Motivated by the positive results of both experiment 1 and Delgado and colleagues (Delgado *et al.* 2008), I developed a follow-up fMRI experiment. Both studies had demonstrated that ER effectively decreases both self-reported pleasant anticipation and striatal EV signals during the anticipation of monetary reward. However, they did not provide evidence that ER can ultimately affect the *motivation to obtain* reward. Such motivation can be inferred from response reaction times (RT) to target stimuli. RT accelerate when preceded by reward-predictive cues (Bindra 1968; Brown and Bowman 1995; Watanabe *et al.* 2001). If distancing attenuated motivation (as indicated by slowing of RT and attenuation of neural RT encoding), where in the striatum or when in the process of "motivation-into-action" conversion (Mogenson *et al.* 1980) would that happen? Would it take place in the VST, at the stage of implicit motivation encoding (Winkielman *et al.* 2005; Berridge 2007), or in the putamen, at the stage of action preparation (Jaeger *et al.* 1993; Boussaoud and Kermadi 1997; Krams *et al.* 1998)? Furthermore, using psychophysiological interaction analysis (PPI), I aimed to determine which of the commonly reported prefrontal distancing areas actually modulate the striatum to bring about such effects. I supposed that the DLPFC was implicated because DLPFC activity correlates with successful downregulation of both SCR and striatal reward signals (Delgado *et al.* 2008). Finally, a common criticism of emotion regulation studies relates to the issue that they do not monitor eye movements/gaze fixation, raising the possibility that participants achieve regulatory success via fixating off-screen (van Reekum *et al.* 2007). To avoid this problem, I modified the MID task in such a way that participants were forced to look at the reward predicting cues.

In sum, I expected that distancing

(I) decreases striatal reward encoding during the anticipation of reward (€1.00 vs. €0.05 reward predicting cues) in the VST

(II) slows down RT to targets that were preceded by €1.00 reward predicting cues

(III) attenuates striatal target RT encoding (either in the VST or in the putamen)

(IV) increases activity in the DLPFC that in turn modulates striatal reward encoding, the latter indicated by a significant DLPFC × reward encoding PPI

2.3 Distancing from smoking and erotic cues in current smokers

Because of the positive results of both experiments 1 and 2, I moved on and investigated whether smokers could learn to reduce their craving for smoking using distancing. Twenty-four current smokers underwent fMRI during which they viewed blocks of smoking-related, erotic-related, or neutral pictures. I supposed that distancing would decrease cue-induced appetitive feelings (sexual lust and craving for smoking) and attenuate smoking as well as erotic cue-induced brain activations. I included erotic pictures in order to investigate whether any regulatory deficiencies observed (as revealed by absence of emotion or signal decreases) were restricted to smoking cues or would apply to other rewards as well (Bickel and Marsch 2001; Buhler *et al.* 2010), owing to addiction-related generalization effects or premorbid impulsivity (chapter 1.2.2). Furthermore, each smoker was tested under two states: smoking as usual and overnight abstinence (≥ 12h). The rationale behind this was that I supposed that any observable failure to regulate would be restricted to abstainers, because temporary abstinence might entail a temporary breakdown of cognitive control abilities caused by increases in craving and smoking cue-induced signals (McClernon *et al.* 2008). Finally, I assessed individuals' FTND score to test whether increases in nicotine dependence—by way of potentiation of striatal smoking cue responses (McClernon *et al.* 2007)—would influence the ability to regulate craving or smoking cue responses.

To sum it up,

(I) I expected that distancing would decrease both smoking and erotic cue-related appetitive feelings as well as smoking and erotic cue-induced neural signals

(II) I supposed that any observable failure to regulate was restricted to a) smoking cues and b) abstinent or heavy smokers

3. General methodology

In all three studies, I used fMRI to measure the neural activity that correlated with experimentally manipulated cognitive processes. In contrast to electroencephalography (EEG) or magnetoencephalography (MEG), fMRI measures neural activity only indirectly via neurovascular coupling: discharging neurons increase local glucose metabolism and oxygen consumption, leading to an increase in deoxyhemoglobin versus oxyhemoglobin concentration in blood-supplying vessels. This is followed by an increase in local blood volume and a blood inflow that oversupplies the activated region with oxygenated blood and that entails a positive oxyhemoglobin to deoxyhemoglobin ratio (Buxton *et al.* 1998; Villringer 2000; Logothetis 2008). FMRI can detect such endogenous changes in blood oxygenation using the BOLD contrast. The BOLD contrast is based on the differential magnetic properties of oxyhemoglobin and deoxyhemoglobin: deoxyhemoglobin is paramagnetic, attracts magnetic field lines, and leads to small inhomogeneities and distortions in the magnetic field of the MRI scanner. By contrast, oxyhemoglobin is diamagnetic and repels magnetic field lines. As a consequence, decreases in deoxy- versus oxyhemoglobin concentration lead to a less distorted magnetic field and a slower fMRI signal decay over time. This is the basic mechanism by which neural activity probably elicits BOLD signal increases, which was first demonstrated in 1992 in humans (Bandettini *et al.* 1992; Frahm *et al.* 1992; Ogawa *et al.* 1992). The typical BOLD response begins with an initial dip that presumably reflects initial increases in deoxyhemoglobin, peaks around 4-6 seconds when oxyhemoglobin concentration saturates, is followed by an undershoot, and returns to baseline at about 20-30 seconds (Henson and Friston 2007). The latency and duration of the BOLD response may differ between brain regions and subjects though (Henson *et al.* 2002). Furthermore, whereas the neural response to an event occurs within a few hundred milliseconds, the accompanying BOLD response unfolds on a very slow time-scale in the order of seconds. This is a disadvantage of fMRI, because it means that underlying neuronal processes are mapped with only a poor temporal resolution. It is mitigated by the fact that, in contrast to EEG and MEG, fMRI has a very good spatial

resolution in the order of a few millimeters. There has been a debate about which kind of neuronal processes BOLD signals actually represent: does the BOLD response reflect the input to or the output of a particular brain area? Several experiments have collected simultaneous microelectrode and fMRI recordings in monkeys to address this question (Logothetis *et al.* 2001; Goense and Logothetis 2008). Microelectrodes can assess input to an area via local field potentials which represent the sum of excitatory and inhibitory postsynaptic potentials on the dendrites of local neurons. In contrast, output of an area can be inferred from increased action potentials which depend on the spiking of projection neurons within that area (Logothetis 2007). The results demonstrated that the fMRI signal correlated with local field potentials but not with action potentials, suggesting that the BOLD signal reflects the input and intra-regional processing in a given brain region rather than its output (Logothetis *et al.* 2001).

In all three studies reported here, I used the statistical parametric mapping software (SPM; Wellcome Trust Centre for Neuroimaging, London, UK) for the analysis of the fMRI data. Data analysis in SPM is subdivided into several sequential steps: preprocessing, first-level analysis, and second-level analysis. Typical preprocessing procedures are slice timing, realignment, normalization, and smoothing (Smith 2001). Slice timing is optional and can be used to correct for differences in acquisition time between slices. Such time differences violate the assumption of first-level models that all data within one volume were acquired simultaneously. During slice timing, the slice data are Fourier-transformed, phase-shifted in the frequency domain to match a reference slice, and reverse Fourier-transformed back to the time domain. Spatial realignment corrects for subject movement during scanning. One volume is selected as the reference image, and all the other volumes of the data set are repositioned using rigid body transformations (i.e., translations and rotations along the three space axes) to spatially align with this image. The estimated realignment parameters are often used as additional regressors in the first-level design matrix to explain remaining movement-related variance. Furthermore, there are substantial inter-individual differences in brain size and shape. To allow analysis of activation patterns on the group level and to assure comparability of results across studies, such inter-individual variability has to be removed. During spatial normalization, images are therefore spatially transformed and warped to match a template image from the standard stereotactic space. Finally, spatial

smoothing is applied to the data. Smoothing aims to capture the most important, low frequency spatial activation patterns in the data, while leaving out the finer-grained noise. Among other tings, smoothing renders the data more normally distributed, and increases the signal-to-noise ratio and thus the statistical power. During smoothing, the data are convoluted with a three-dimensional Gaussian kernel. The full width at half maximum of the kernel in mm specifies the degree of weighted local averaging applied: the greater the kernel, the greater the number of neighbouring voxels that contribute to the calculation of the voxel's new intensity value. Typically, kernels of 3-4 times the original voxel size are applied for the intention of group analyses.

After the preprocessing, the data are ready for statistical analysis. During first-level analysis, a mass univariate general linear model (GLM) approach (Cohen 1968) is adopted to predict the signal time course at each voxel separately. More precisely, the SPM GLM models the participant's data as a linear combination of weighted regressors, a residual error term, and a constant (Kiebel and Holmes 2007). In the specified GLM design matrix, each regressor corresponds to one experimental condition. For each regressor, a predicted BOLD signal time course is generated by convoluting the stimulus function (i.e., the time points at which the experimental condition was present) with the canonical hemodynamic response function (HRF) (Henson 2007). The HRF mimics the BOLD response by combining two gamma functions that model the peak and undershoot of the BOLD response, respectively (Friston *et al.* 1998). During model estimation, a regression weight is estimated for each regressor at each voxel and written into a beta-image (one image for each regressor). The beta value of a given regressor at a specific voxel reflects the degree to which this voxel is activated by the underlying experimental condition. The estimated beta values can then be used to test hypotheses using contrasts (Poline *et al.* 2007), for instance, whether one condition leads to activation different from zero (contrast on one beta value), or whether activation differs between conditions (differential contrast on two or more beta values). In the case of a *t*-contrast, the voxel-wise contrast values are written into a contrast-image. In the case of a *F*-contrast, SPM computes the explained variance (extra sum of squares) attributable to the regressors included in the contrast: it does so by subtracting the residual sum of squares of the full model (RSS) from the residual sum of squares of a reduced model that does not contain those regressors. The resulting voxel-wise values are written into

an ess-image. Once the contrast is tested via the SPM user interface, the contrast and ess values are divided by the standard deviation (*t*-contrast) and RSS (*F*-contrast), respectively, producing *T*-images or *F*-images. The resulting statistical map displays voxels which are activated given both the linear combination of regressors and a pre-specified significance level α (i.e., voxels which *p*-value falls below α). Because the statistical tests are carried out voxel-wise, this amounts to roughly a several hundred thousand tests per contrast. Therefore, to control the rate of false positives, some correction for multiple comparisons is mandatory. The commonly used Bonferroni correction entails far too conservative corrected thresholds for fMRI data, because it assumes complete independency between tests. In fact, such independency is illusory, as the preprocessing (realignment, normalization, and smoothing) introduces considerable spatial correlation, that is, dependency, between voxel intensity values. Fortunately, SPM offers more suitable procedures that are based on random field theory, take into account the extent of spatial correlation (smoothness) within the data set, and find appropriate and sensitive family-wise error (FWE) corrected thresholds (Worsley *et al.* 1996; Brett *et al.* 2007).

If the intention is to do statistical inference on a group level, then the contrast-images of the first-level analysis enter a second-level analysis. A variety of parametric procedures is available in SPM for the testing of group effects, among them *t*-tests, multiple regressions, and analyses of variance (ANOVA). I chose the latter as the method of choice in my experiments, because it allowed me to conduct multiple tests (main effects, simple main effects, interactions) within just one design. Another advantage of the SPM ANOVA was that it corrects for violations of sphericity which in my studies resulted from repeated measurements of the same individuals.

4. Dissertation projects

4.1 Study I: Distancing from monetary reward in healthy participants

In the first study of this thesis, I used fMRI and a modified version of the MID task (Knutson, Adams *et al.* 2001) to investigate whether distancing attenuates positive feelings as well as VST BOLD signals that accompany both the expectation and the receipt/omission of monetary reward.

4.1.1. Experimental design

Sixteen subjects (8 males) without any history of medical or neurological illness or regular intake of medicaments participated in the experiment. At the beginning of each MID trial, participants saw an abstract cue that indicated the amount of money (€0.50, €0.10) to be won. Following an *anticipation period* of 3.75 seconds, a target (square or triangle) appeared on the screen. By pushing the correct target-assigned button (right thumb/square, right index finger/triangle) within a fixed interval of 1 second, subjects became eligible to win the announced amount of money. Immediately after the button press, during the *outcome period*, participants were informed whether they had won (€0.50, €0.10) or not (€0.00). The latter were omission trials (40 %), where rewards were withheld despite correct responses. The anticipation period allows investigation of cue-bound EV signals (predicted magnitude × predicted win probability of 60 %), whereas the outcome period allows investigation of PE signals (calculated as the outcome actually received minus the EV). Blocks of 5 MID trials were preceded by a written cue that instructed subjects either to permit all upcoming reward-related feelings (eager anticipation of as well as pleasure upon winning monetary reward) or to distance themselves explicitly from them. Blocks were followed by the display of a rating slider which participants used to specify the intensity of feelings they had experienced within the preceding block. Prior to scanning, participants completed a 15 minutes training

version of the task in which they learned the predictive values of the cues as well as the distancing strategy itself.

4.1.2. Results and discussion

Distancing from as compared to permitting feelings reduced self-reported positive feelings, replicating the finding from Delgado et al. (Delgado *et al.* 2008). It also concurs with previous studies that showed that distancing decreases negative (Ochsner *et al.* 2002; Kalisch *et al.* 2005; Eippert *et al.* 2007; Walter *et al.* 2009; Koenigsberg *et al.* 2010; Schardt *et al.* 2010) and positive affect (Kim and Hamann 2007) as well as sexual lust (Beauregard *et al.* 2001). Thus, our result supports the hypothesis that participants are able to downregulate their *subjective experience* of emotion in a monetary reward environment.

Analyzing BOLD signals that related to the anticipation period, I identified a cluster in the right VST that encoded the EV when participants permitted feelings. Such encoding was abolished during distancing (interaction EV × strategy). To test possible ER effects on PE signals, I applied a parametric modulation analysis (Buchel et al. 1996). Events during the outcome period were classified into one of two categories depending on the ER strategy applied: permit or distance (0^{th} order regressors). Individual trial-by-trial PE values were then input into the model as parametric modulators (1^{st} order regressors) of the respective 0^{th} order regressors, enabling me to compare linear PE encoding between strategies (permit, distance). Using one-sample and paired *t*-tests on the 1^{st} order predictors, I found that the left VST encoded PE linearly during the permit condition. This PE encoding activity was attenuated during ER, mainly driven by a modulation of the most salient outcome signals: in comparison to the permit condition, distancing lowered and elevated €0.50 win and omission PE, respectively, so that €0.50 win versus omission coding was lost. The right VST showed a trend toward PE attenuation. Our observation of temporary EV elimination in the VST replicates the finding of Delgado et al. (Delgado *et al.* 2008) who proved that ER attenuates neural encoding of reward expectation. With our additional observation of temporary PE elimination, we show for the first time that ER not only alters reward signals during the expectation, but also during the outcome period. These findings are of

particular relevance: in the introduction I have pointed out that EV and PE signals support Pavlovian and instrumental learning in non-drug as well as in drug contexts. However, they are still present when behavior is highly overtrained and fixed strategies have been adopted, as in this study (Bayer and Glimcher 2005; Abler *et al.* 2006) If to-be addicts could learn to decrease drug CS-related EV signals in the VST via ER, this could presumably lower the predictive value of the CS, diminish cognitive urges that arise from VST-bound implicit wanting, and ultimately prevent drug seeking behavior. Furthermore, it has been hypothesized that drug-induced dopamine increases generate extra large PE during drug receipt (Redish 2004). These abnormal PE lead to excessively optimistic EV predictions, and in so doing intensify drug pursuit. If addicts could learn to regain control over aberrant PE signals within the VST, this would constitute another way to lower the EV of the drug CS.

In sum, I demonstrate in this experiment that, using ER, participants are able to attenuate reward-related emotion experience as well as neural signals underlying reward computation. Unfortunately, it does not necessarily follow that distancing ultimately affected participants' *motivation to obtain* reward: although the analysis of target RT—an objective marker of motivated behavior (Bindra 1968; Brown and Bowman 1995; Watanabe *et al.* 2001)—revealed an interaction between predicted reward levels (€0.50, €0.10) and strategy (permit, distance), €0.50 target RT were not significantly faster than €0.10 target RT when compared in the permit condition alone. Therefore, we cannot be sure that ER altered motivation, as the experimental setting did not seem to have generated considerable *differential* motivation to begin with. As a consequence, further experiments are required to substantiate this assumption. Such experiments should use greater reward differences, force subjects to look at reward predicting cues, and provide subjects with the opportunity to control the outcomes fully so as to elicit stronger motivational states.

Distancing as compared to permitting feelings increased activity in several brain regions in the right hemisphere, including the DLPFC, dACC/rostral cingulate zone (RCZ), lateral OFC, and inferior parietal lobe/temporal parietal junction (IPL/TPJ). Such an activation pattern has been observed in numerous experiments that investigated distancing in fMRI environments (Beauregard *et al.* 2001; Kalisch *et al.* 2005; Urry *et al.* 2006; Eippert *et al.* 2007; Johnstone *et al.* 2007; Kim and Hamann 2007; Walter *et*

al. 2009; Erk *et al.* 2010; Schardt *et al.* 2010). The right TPJ/IPL is involved in the relocation of attention (Corbetta and Shulman 2002) as well as in switches from an ego- to an allocentric perspective (Vogeley and Fink 2003). Hence, TPJ/IPL activity suggests that subjects may have tried to assume the position of a neutral, distant observer. The DLPFC is perhaps the most commonly reported area in emotion regulation studies using reappraisal. As already described in chapter 1.1.2, DLPFC (BA 9/46) activity has been implicated in self-control (Knoch *et al.* 2006; Hare *et al.* 2009; Figner *et al.* 2010), presumably by way of linking of short-term memory representations to rule-based or goal-directed action selection (Smith and Jonides 1997; Bunge *et al.* 2002; Jiang and Kanwisher 2003; Ridderinkhof, van den Wildenberg *et al.* 2004). In the present experiment, ER instructions had to be kept in mind and linked to EV and PE presentations in order to implement successful top-down modulation of the latter. Remarkably, conjoint activation of the TPJ/IPL and DLPFC has been shown to distinguish attempts of decreasing feelings from attempts of increasing feelings during the reappraisal of emotional material (Ochsner *et al.* 2004). Activity in the RCZ can be interpreted in terms of detection of response conflict (Dreher and Grafman 2003; Ridderinkhof, Ullsperger *et al.* 2004; Ridderinkhof, van den Wildenberg *et al.* 2004) Such conflict surely arose from two competing response tendencies: DLPFC-governed intentions to detach, and bottom-up EV and PE signals from mesolimbic neurons that normally promote conscious hedonic reward experience in the ACC and OFC, respectively (Berridge 2003; Kringelbach 2005). The lateral OFC has been implicated in the revaluation of learned stimulus-response associations in reversal learning paradigms (O'Doherty, Critchley *et al.* 2003; Remijnse *et al.* 2005; Ghahremani *et al.* 2010) as well as in the active updating of the motivational relevance of stimuli (Bechara *et al.* 2000; Rolls 2000). Therefore, both reduction of emotion experience and inhibition of EV and PE could have been accomplished via involvement of the lateral OFC. Indirect support for such a view comes from the observation that in the current experiment, self-reported reappraisal success (decrease of feelings) showed a trend toward positive correlation with ER-related activation increases in the lateral OFC and RCZ, which is in agreement with two previous studies (Eippert *et al.* 2007; Kim and Hamann 2007). As for EV and PE signals, lateral OFC might have revaluated these signals and propagated them back to the VST, or directly inhibited VST EV and PE signalling, both via the affective OFC-

VST loop. A similar role for the lateral OFC has been proposed in the context of distancing from negative picture content and blunted amygdala responses (Ochsner *et al.* 2004; Urry *et al.* 2006; Eippert *et al.* 2007; Johnstone *et al.* 2007). However, only studies that deploy functional or effective connectivity analyses (Friston *et al.* 1997; Friston *et al.* 2003; Stephan 2004) will definitely answer the question which ER areas contribute to top-down control over reward processing, which was consequently one of the focuses of the follow-up experiment.

4.2 Study II: Functional connectivity changes during the regulation of reward motivation in healthy participants

In the second study of this thesis, I aimed to determine whether distancing may attenuate individual motivation to obtain monetary reward using fMRI and a mixed MID/memory task. Furthermore, I investigated the role of PFC regions in the modulation of striatal reward anticipation signals using PPI.

4.2.1 Experimental design

A total of 24 subjects (11 males) without any history of medical, psychiatric, or neurological illness or regular intake of medication participated in the study. At the beginning of the MID trial, subjects saw a cue (coin) that indicated the amount of money (€1.00 vs. €0.05) to be won, followed by a delay period of 3 seconds. Participants were instructed to look at and to memorize the announced expected reward. A target consisting of 2 white balls displaying the 2 possibly announced reward magnitudes ("100" = €1.00, "005" = € 0.05) then appeared on the screen. Participants had to report the memorized expected reward by choosing the respective ball and pushing the assigned joystick button within 750 milliseconds to become eligible to win the announced amount of money. Thus, participants were forced to look at the reward predicting cues so that possible ER effects could not be explained by avoidance of stimulus processing. After the target period, participants were informed whether they had pushed the correct button (target ball turning green) or not (target ball turning red). Subjects were told in advance that only 60 % of the correct responses were paid off after the experiment. Blocks of 5 trials were preceded by a written cue that instructed subjects either to permit all upcoming reward-related feelings of pleasant anticipation (permit strategy) or to distance themselves explicitly from them (distance strategy). At the end of the experiment, subjects rated on a 7-point Likert scale how much the reward cues had evoked feelings of pleasant anticipation in the different regulation conditions. Prior to scanning, subjects were taught the distancing strategy and completed a 20 minutes training of the task.

4.2.2 Results and discussion

Distancing significantly diminished the anticipation of reward as indicated by retrospective permit versus distance ratings. It also slowed down €1.00 target RT exclusively, suggesting a reduction in motivation to obtain high reward. During the anticipation of reward (spanning the cue plus delay period), distancing increased activity in the right IPL/TPJ, right DLPFC (BA 9), and left middle temporal gyrus. This was accompanied by a loss of differential encoding of expected reward (€1.00 > €0.05) in the left putamen, as evidenced by a significant interaction of ER (distance, permit) × expected reward (SPM ANOVA), replicating the finding from study 1. Furthermore, I investigated whether striatal activity during the anticipation period reflected the observed RT effects. Individual trial-by-trial RT values were used as parametric modulators (1st order regressors) of the neural anticipation signals (0th order regressor) during permit and regulate trials separately. Differences in linear encoding of RT between strategies (permit > distance) were tested with a paired *t*-test on 1st order regressors. I found activation in the right and left putamen, the latter cluster located slightly more ventrally than the ANOVA interaction maximum. Plotting group averaged parametric responses allowed me to visualize this effect: putamen activity during the anticipation of reward linearly encoded subsequent RT during permit: higher activity predicted faster RT (and vice versa). During reappraisal, the putamen did not correlate with RT.

In sum, our results support the hypothesis that ER reduces behaviorally measurable motivation to obtain reward which I regard as a conditio sine qua non for it being once a promising tool to effectively prevent drug pursuit (see discussion study I). I further aimed to determine where in the striatum ER would impact EV and RT encoding. Interestingly, and to some degree contradictory to Delgado's and my previous finding (Delgado *et al.* 2008), reward encoding within the affective ACC-VST loop was not affected by ER. Instead, ER attenuated EV and RT encoding in two adjacent clusters in the left putamen. First, EV-related activation of the putamen is in accordance with previous studies that implicated this region in the anticipation and evaluation of reward (McClure *et al.* 2003; Preuschoff *et al.* 2006). Such cue-related information can reach the putamen via striato-nigro-striatal spiral loops (Haber *et al.* 2000; Groenewegen and

Trimble 2007) originating in VST or via diffuse projections from the affective ACC-VST loop (Haber *et al.* 2006; Draganski *et al.* 2008). Second, RT-related activation of the putamen in turn concurs with its proven involvement in action selection, preparation, and initiation (Jaeger *et al.* 1993; Boussaoud and Kermadi 1997; Krams *et al.* 1998). Therefore, in the current experiment, the putamen most probably was a site where reward cue information could actually provide motor preparation with motivational loading and so facilitate ensuing action. Consequently, ER-induced elimination of EV and RT coding in the putamen but not the VST suggests that ER did not necessarily alter motivation per se but definitely prevented *motivational loading of action* (Mogenson *et al.* 1980). As for unaffected EV signals in the ACC-VST, comparing task demands may resolve the apparent contradiction between the current and previous experiments: in both study 1 and Delgado et al. (Delgado *et al.* 2008), maintenance of reward cue information was not mandatory. Thus, both experiments allowed subjects not to process this information at all. In the present study, however, subjects were forced to look at the reward predicting cues and to map reward magnitudes onto targets in order to be able to show a correct response. I suspect that such task demands inevitably led to unaffected stimulus-outcome representations in the VST-ACC that were propagated to the putamen, no matter what strategy (permit or regulate) was applied.

To investigate the role of ER areas in the modulation of reward anticipation, I set up a PPI. The basic assumption of PPI is that the BOLD signal y_1 in a to-be-identified region can be explained by an interaction between physiological activity y_0 in a seed region and a psychological or contextual factor u (Friston *et al.* 1997; Stephan 2004):

$$y_1 = ay_0 + b(y_0 \times u) + cu + X\beta \qquad (4)$$

where the bilinear term $b(y_0 \times u)$ refers to the degree b to which activity in y_1 can be explained by the aforementioned interaction between y_0 and u (calculated as the element-by-element multiplication between both vectors). a denotes the context-independent strength of connection between the seed region and y_1, cu describes the strength of direct influence of the contextual factor on y_1, and β denotes the influence of confound variables X *on* y_1. Ideally, both the seed and the target region appear in a PPI-

preceding categorical ANOVA, with, for instance, the seed region showing a main effect of factor A and the target region showing an interaction between factors A and B. There are then two alternative perspectives on PPI: 1) the psychological or contextual factor B modulates the contribution of the seed region to the target or 2) contribution from (i.e., level of A-related activity in) the seed region modulates the responsiveness of the target to the contextual factor B (Friston *et al.* 1997). In this study, I referred to the latter reading and expected that activity in the striatum during reward anticipation was a function of activity in the DLPFC (that showed a main effect of ER) × the contextual factor of expected reward (€1.00 vs. €0.05), resulting in the observed striatal interaction pattern ER × expected reward. More precisely, I assumed that the striatum would differentiate between €1.00 and €0.05 cues if, and only if, DLPFC activity was low.

Of the three observed ER areas, the DLPFC is the only one projecting directly to the striatum (Lehericy *et al.* 2004; Haber *et al.* 2006; Postuma and Dagher 2006; Draganski *et al.* 2008) and was consequently chosen as the PPI seed region (please refer to the paper for technical details). A negative influence of the DLPFC on expected reward was tested with a one-sample *t*-test on the PPI.ppi regressor at the group level [-1]. Again, I observed activity in the left putamen, overlapping with activations from the ANOVA interaction cluster. Technically, this *t*-test revealed a difference in regression slopes between €0.05 and €1.00 trials in the regression of DLPFC on putamen activity. To determine the signs of the respective slopes, I computed group mean slopes and constants for both €0.05 and €1.00 trials. This exploratory analysis revealed that the slope for €1.00 trials was not negative but only less positive than for €0.05 trials. Thus, the PPI result was consistent with the idea that the DLPFC contributed to the attenuation of reward encoding by amplifying €0.05 cue responses rather than by inhibiting €1.00 cue responses.

To sum it up, a main objective of the present study was to determine whether regulatory effects on reward encoding were a consequence of top-down modulatory influence from the PFC. Accordingly, the PPI analysis revealed that increases of DLPFC activity came along with diminished anticipatory reward cue encoding in the left putamen. Moreover, PPI and ANOVA activations overlapped substantially, indicating that the DLPFC exerted its influence at the very site where ER effects were actually taking place. A modulatory influence of the DLPFC concurs with previous

reports that demonstrated that BA 9/46 projects to anterior (Lehericy *et al.* 2004; Haber *et al.* 2006; Postuma and Dagher 2006; Di Martino *et al.* 2008) and posterior (Draganski *et al.* 2008) aspects of the putamen. The PPI activation was furthermore located at the intersection of associative and sensorimotor putamen (MNI *y* coordinate ~0) (Alexander *et al.* 1990). Thus, our finding is in accordance with the concept of convergence zones, in which PFC fibers from different cortico-basal ganglia circuits converge and in so doing permit information exchange among the circuits, in this case between the associative and the sensorimotor loop (Joel and Weiner 1994; Haber and Knutson 2010).

However, there are two limitations to our finding that should be duly mentioned. First, PPI analyses are regression-based and do not allow conclusions about causality. Thus, it is not possible to infer a causal role for the DLPFC from the present PPI finding. For instance, we cannot rule out that a third unknown brain region was the real cause of the observed DLPFC-putamen effects. Causal influences can only be properly determined via effective connectivity methods (Stephan 2004). To corroborate the PPI finding, I therefore applied additional Dynamic causal modeling analyses (Friston *et al.* 2003). Unfortunately, these analyses did not yield significant results. Consequently, the present findings are merely consistent with the idea that the DLPFC exerted modulatory control over reward encoding.

Second, theoretically, the DLPFC is in position to amplify as well as to inhibit putaminergic output via efferents to the direct and indirect cortico-basal ganglia pathways, respectively (Frank *et al.* 2004; Aron *et al.* 2009). However, whereas the ANOVA analysis demonstrated an inhibitory influence of ER on high reward, the PPI results indicated that the DLPFC contributed to such regulation not via inhibition of high reward but solely via amplification of low reward. Thus, although inhibition of high reward was surely present in the brain, we could not detect the neural source of such inhibition. Nevertheless, amplification of low reward responses is consistent with task instructions that required subjects to disengage from any upcoming emotions. During nonregulation, subjects might have perceived €0.05 cues as aversive and actually experienced negative feelings. Conversely, successful disengaging from emotion could have led subjects to appraise low reward cues as less negative, and the

putative DLPFC modulation of putamen low reward responses could reflect such reappraisal.

4.3 Study III: Distancing from smoking and erotic cues in current smokers

In the third study of this thesis, using fMRI and a cue reactivity paradigm (Drummond *et al.* 1995), I investigated whether distancing is suitable to decrease smoking cue-related craving as well as smoking cue-induced neural signals in current smokers. Furthermore, I investigated whether temporary abstinence and degree of nicotine dependence influence possible ER-effects in a negative way.

4.3.1 Experimental design

Twenty-four light to heavy dependent current smokers (13 males) participated in the study. Smokers were required to have smoked at least 10 cigarettes per day for at least 5 years. All subjects were free of current medical, neurological, and DSM-IV psychiatric disorders, as measured by the Mini International Neuropsychiatric Interview (Ackenheil et al. 1999).

Smokers were tested on two separate days under two conditions (between-subject counter-balanced order): smoking as usual and overnight withdrawal (≥12 h). On each test day, subjects completed two runs while undergoing fMRI: In the first run, participants saw blocks of smoking and blocks of smoking cue-matched neutral pictures. In the second run, they saw blocks of erotic and blocks of erotic cue-matched neutral pictures (for a description of stimulus material, please see Supplemental Material and Methods of the paper). Prior to each block, a display instructed subjects either to permit all upcoming feelings ("permit") or to distance themselves explicitly from them ("regulate"). Participants were told not to close or avert their eyes during either strategy. To ensure maintenance of attention (McClernon *et al.* 2007), subjects had to press a button whenever a new picture or instruction appeared on the screen. On each day, subjects underwent 20 minute distancing training sessions directly before entering the scanner. At the end of the fMRI experiment, subjects rated the degree of their retrospective appetitive feelings (sexual arousal or craving for smoking) in the different regulation conditions. Furthermore, before each scanning session, participants completed self-report questionnaires on mood, craving, and withdrawal symptoms.

Subsequently, blood and breath samples were taken to verify overnight abstinence on the abstinence day.

To exclude that ER effects in smoking cue-reactive and erotic cue-sensitive regions were mainly driven by up-regulation of neutral cue responses, we tested ER effects as an exclusive downregulation of *valent* cue responses (i.e., smoking cues $_{Permit}$ > smoking cues $_{Regulate}$ or erotic cues $_{Permit}$ > erotic cues $_{Regulate}$, respectively). Smoking cue reactivity was defined as smoking cues $_{Permit}$ > smoking cue-matched neutral cues $_{Permit}$ (Brody et al. 2007; McClernon et al. 2007; Vollstädt-Klein et al. 2011), erotic cue sensitivity was defined as erotic cues $_{Permit}$ > erotic cue-matched neutral cues $_{Permit}$ (Karama et al. 2002; Hamann et al. 2004). Tests of ER effects were then restricted to smoking cue-reactive and erotic cue-sensitive regions via inclusive masking with the latter contrasts.

4.3.2 Results and discussion

Smokers smoked an average of 17 cigarettes per day (range 10 - 25) and had smoked for an average of 13 years (range 9 - 21). Mean FTND score was 3.9 (range 1 - 7). Breath CO levels were significantly lower during abstinence, as were serum cotinine concentrations, which indicated that subjects had significantly reduced their nicotine consumption before the abstinence day. Abstinence led to significantly greater cigarette craving scores as measured with the questionnaire on smoking urges (Tiffany and Drobes 1991) and withdrawal symptoms according to ICD-10 International Classification of Diseases F17.3 assessment (WHO 1993).

Using distancing, smokers were able to decrease cue-induced subjective sexual arousal as well as craving for smoking, although sexual arousal was regulated more effectively. Degree of nicotine dependence and abstinence did not impair the ability to regulate either cue class. In the brain, ER decreased erotic cue responses in the left caudate and hippocampus as well as smoking cue responses in the right VMPFC, independent of smoking state. Abstainers showed enhanced smoking cue responses as compared to satiety in the left caudate and amygdala which they were able to downregulate as well. In the left caudate though, ER-related reductions of smoking cue responses decreased with increasing FTND score.

Downregulation of behavioral and neural responses to smoking and erotic cues is in accordance with Kober et al. (Kober *et al.* 2010) who had demonstrated that short-time abstainers are able to decrease both smoking cue-induced cravings and accompanying ventral striatal signals using ER. Here, we extend the previous finding by showing that ER effects on craving for smoking and neural smoking cue responses still hold under conditions of prolonged abstinence when craving becomes intense. Given the ability of smoking CS to trigger craving and relapse (Niaura *et al.* 1988; Shaham *et al.* 2003; Tong *et al.* 2007; Ferguson and Shiffman 2009; Janes *et al.* 2010), this positive finding is particularly promising: it suggests that trained ER skills may actually enable smokers to control neural smoking cue responses and craving when they try to quit smoking. Of course, further studies under field conditions are required to definitely prove this. Nevertheless, training in the cognitive regulation of craving is already one of the focuses of cognitive-behavioral therapy interventions in smokers (Drummond *et al.* 1995; Dutra *et al.* 2008). However, there is also a caveat to the current findings: ER reduced sexual arousal more effectively than craving for smoking. Thus, it follows that it might require more extensive distancing training to affect drug craving to the same degree as craving for non-drug rewards, a fact that should be taken into account by interventions that use distancing.

ER attenuated smoking cue-induced responses in smoking state-independent (VMPFC) as well as in abstinence-specific (caudate and amygdala) brain regions. Furthermore, in abstainers, degree of craving correlated with smoking cue-induced activations in the caudate head and amygdala, whereas degree of craving reduction correlated with signal reductions in the subgenual ACC. All four regions have been associated to some degree with motivational aspects of nicotine addiction such as drug craving or drug valuation (McClernon *et al.* 2005; Franklin *et al.* 2007; Wang *et al.* 2007; McClernon *et al.* 2008; Kober *et al.* 2010; Koob and Volkow 2010; Chase *et al.* 2011). Moreover, as noted earlier (see chapter 1.1.2), there is evidence for a circuit linking the VMPFC and caudate that mediates goal-directed valuation and action in healthy controls (Chib *et al.* 2009; Hare *et al.* 2009; Wunderlich *et al.* 2009; Balleine and O'Doherty 2010). Consequently, but hypothetically, reduction of smoking cue responses in the VMPFC-caudate could reflect reduction of excessive salience or value attribution to smoking cues. In sum, I conclude that ER exerted its regulatory influence

on craving and smoking cue responses in regions that have been identified as major contributors to the maintenance of nicotine addiction.

The effectivity of ER to reduce abstinence-specific caudate smoking cue responses tended to decrease with degree of nicotine dependence, indicating that heavy smokers were not able to reduce smoking cue-induced signals in this area. This deficit was not a result of enhanced or decreased smoking cue responses per se, because smoking cue responses during nonregulation did not vary with FTND. Furthermore, a comparable negative influence of nicotine dependence was not present in satiated smokers or during the regulation of erotic cues. In sum, these results speak for an abstinence- and drug-specific deficiency in heavy smokers. It is difficult to interpret this deficiency in functional terms though. In any event, it does not reflect an inability to diminish the subjective experience of craving: degree of nicotine dependence did not influence the regulation of self-reported craving for either cue type, and caudate activity did not correlate with craving or craving reductions to begin with (craving correlations in the caudate were located more dorsolaterally). For an interpretation of this caudate finding, I refer the reader to the general discussion section (chapter 5.3), where I discuss it in light of addiction theories and recent evidence from animal and human research.

The regulation of smoking and erotic cues led to conjoint activity in the DLPFC, VLPFC, DMPFC, and dACC, in accordance with previous studies on reappraisal of erotic pictures (Beauregard et al. 2001), negative pictures (Ochsner and Gross 2005; Eippert et al. 2007), non-drug rewards (Delgado *et al.* 2008), and smoking cues (Kober *et al.* 2010). This suggests that smokers in the current study accomplished ER in a similar way as healthy controls in previously reported ER experiments. Furthermore, I applied post-hoc analyses of eye vitreous fMRI activations (Beauchamp 2003) as well as frontal eye field region-of-interest analyses (Paus 1996). These methods can be used to detect differences in eye movements between experimental conditions. Both analyses did not yield evidence that ER effects on cue-sensitive regions had been accomplished by avoiding picture content (e.g., by fixating off screen).

5. General discussion

In this dissertation, I investigated three important questions: (a) Is ER suited to regulate reward-related desires and motivation as well as neural signals that underlie the computation of reward? (b) What are the neural processes that underpin successful regulation of reward? (c) Can smokers use ER to successfully regulate craving and smoking cue reactivity? In the final section, I will return to these questions, discuss the findings in a broader context and relate them to theories on ER and nicotine addiction, address methodological issues for ER research, and make suggestions for holistic ER interventions in smoking cessation.

5.1 Emotion regulation effects on reward

In study I, I have shown that distancing reduces feelings of anticipation and pleasure in the context of monetary reward, replicating the shortly before published findings of Delgado et al. (Delgado *et al.* 2008). Both studies proved that ER is not only suited for the regulation of negative feelings (Ochsner *et al.* 2002; Kalisch *et al.* 2005; Eippert *et al.* 2007; Walter *et al.* 2009; Koenigsberg *et al.* 2010; Schardt *et al.* 2010) but can be used to regulate reward-related feelings as well, thus extending the scope of application of ER. Furthermore, they demonstrated that an ER strategy that aims at reducing *reward emotion experience* also diminishes ventral striatal signals that underlie the *computation of reward* (i.e., EV and PE signals) in learning and post-learning environments (Bayer and Glimcher 2005; Preuschoff *et al.* 2006). This challenges the notion of a mesolimbic system that processes reward purely automatically and that cannot be accessed or influenced by cognitive control mechanisms. On the contrary, the results suggest that healthy subjects that are willing to modify disagreeable reward-related behavior (e.g., excessive consumption of sweets) may use distancing to reduce EV signals pertaining to reward predicting cues (e.g., the sight of a chocolate bar) and may diminish craving for rewards. Furthermore, extending the Delgado results, I found that ER not only affects the reward expectation, but also modulates emotion experience and PE signals at the time of reward receipt. Thus, even when healthy subjects, for instance, dieters, would

not resist the temptation to approach reward, they would still have the chance to regulate how much pleasure they experience during reward consumption. Furthermore, as PE are used to update the EV of a given reward predicting cue, distancing-related modulation of PE signals during reward consumption would be another option of altering the EV of reward predicting cues. As noted earlier (see chapter 4.1.2), addicts may benefit from distancing in much the same way: if drug-induced, extra large PE within the VST really contributed to the learning of excessively optimistic EV predictions (Redish 2004), attenuation of PE signals via distancing could lower the EV of the drug CS, diminish cognitive urges that arise from VST-bound implicit wanting, and possibly diminish drug seeking behavior.

Eminent emotion researchers have pointed out that emotions alter response tendencies, that is, *motivation*, and that the capacity to do so is a central defining component of emotion itself (Scherer 1984; Frijda 1987). In fact, the flexibility of elicited motivated actions constitutes emotion's great advantage for adaptive functioning (Ellsworth and Scherer 2003; Ochsner and Gross 2005). Many reappraisal studies under laboratory conditions focus on the regulation of *emotion experience*, sometimes validating effects by showing simultaneous regulation of *central or peripheral physiology*, and assume that decreased emotion experience—were it to be replicated in a natural environment—would translate into changed behavior. Of course, this is not necessarily true. For instance, exposing social phobics to pictures of harsh facial expressions (Goldin, Manber *et al.* 2009) or negative self-beliefs (Goldin, Manber-Ball *et al.* 2009) and demonstrating decreases of negative emotion via ER does not imply that these subjects will ever act more confidently in their private lives. For ER effects on reward, I think this is an essential point. Consequently, I demanded that for ER to prove effective, it must alter behaviorally measurable motivation to obtain reward under laboratory conditions. Interpreting behavioral RT as an indicator of motivation (Bindra 1968; Brown and Bowman 1995; Watanabe *et al.* 2001), I could prove that distancing diminishes the effort to obtain high reward. Moreover, I identified the putamen as the neural locus of RT encoding as well as of ER-induced attenuation of RT encoding, an observation that is consistent with its implication in action selection, preparation, and initiation (Jaeger *et al.* 1993; Boussaoud and Kermadi 1997; Krams *et al.* 1998). These findings justify optimism that ER may reduce motivation or

motivational loading of reward-related action (Mogenson *et al.* 1980). I think this approach is a step in the right direction if we want to increase the applicability or generalizability of ER effects in the lab. We have to prove that ER alters emotion experience *and* emotion-driven action (motivation). One option is to find measures that reflect response tendencies under laboratory conditions. Another option would be to test ER effects directly under field conditions.

Given the variety of activations that are observed during ER—activations so diverse as to encompass the DLPFC, VLPFC, DMPFC, RCZ, dACC, OFC, lateral OFC, and IPL/TPJ (Beauregard *et al.* 2001; Kalisch *et al.* 2005; Urry *et al.* 2006; Eippert *et al.* 2007; Johnstone *et al.* 2007; Kim and Hamann 2007; Wager *et al.* 2008; Walter *et al.* 2009; Erk *et al.* 2010; Schardt *et al.* 2010)—this speaks against a universal, 'omnipotent' ER center in the brain, but suggests that the specific network activated reflects multiple cognitive processes going on in parallel. The network itself may further reflect specific characteristics of (a) the strategy trained (b) the emotional material to be regulated and (c) the heterogeneity of the sample (or, diversity of particular cognitive strategies) under investigation. Therefore, it is imperative that ER researchers aim at identifying how each of the reported ER areas contributes exactly to ER. We cannot do this by simply reporting activations from categorical ANOVA and by assigning cognitive processes to these activations—this would result in reverse inference (Poldrack 2006). What we should do though is to correlate behavioral variables of the individual—be they measured directly or derived from computational models (O'Doherty *et al.* 2007)—with neural activations and identify *neural markers* of ER and of its subcortical effects. Using this approach, I could show that self-reported decreases in anticipation and pleasure correlated with ER-related increases in lateral OFC and RCZ activity, in agreement with two previous reports (Eippert *et al.* 2007; Kim and Hamann 2007).

To gain a detailed insight into the *neural mechanisms* of ER, we should further determine the exact nature of cortical-subcortical interactions. To this end, ER researchers have begun to apply sophisticated methods like pathway mapping analysis (Wager *et al.* 2008; Kober *et al.* 2010) or functional and effective connectivity analyses such as PPI (Friston *et al.* 1997), structure equation modeling (Buchel and Friston 1997), and DCM (Friston *et al.* 2003). Therefore, I defined that a main objective of this

dissertation would be to elucidate the neural mechanisms by which ER effects regulation of reward. In study II, using PPI I could show that the DLPFC contributes to successful regulation of reward expectation by modulation of putamen reward responses. As noted before, a modulatory influence of the DLPFC on the striatum concurs with previous evidence on DLPFC-striatal connectivity patterns (Lehericy *et al.* 2004; Haber *et al.* 2006; Postuma and Dagher 2006; Di Martino *et al.* 2008; Draganski *et al.* 2008). Moreover, a recent study revealed that the capacity of reward cues to activate the striatum (here: the VTA and NACC) depended quintessentially on reward-induced activation of top-down connections from the DLPFC to these areas (Ballard *et al.* 2011), lending indirect support to my findings. However, although the DLPFC contributed to the modulation of reward, it did so in an unexpected way, namely by amplification of low reward. And although inhibition of high reward was surely present in the brain, I could not detect the neural source of such inhibition. Thus, strictly speaking, the neural mechanisms by which ER regulates high reward remain unclear. Nevertheless, the results shed further light on the mechanisms of prefrontal-subcortical interactions during ER, extending previous findings about DLPFC's involvement in the regulation of amygdala signals in aversive contexts (Erk *et al.* 2010; Schardt *et al.* 2010) to the domain of reward regulation.

5.2 Emotion regulation effects on craving for smoking

It has been hypothesized (see chapter 1.2.2) that long-time drug taking induces neuroplastic changes within the PFC (Volkow *et al.* 1991; Liu *et al.* 1998; Jentsch and Taylor 1999; Tabibnia *et al.* 2011) and that these changes cause diminished activity in prefrontal regions that are involved in self-control (Goldstein and Volkow 2002; Volkow *et al.* 2004). The so-acquired impairment in self-control is supposed to result in an inability to inhibit strong motivational and habitual impulses that are triggered by drug CS which may further promote the compulsive drug pursuit (Jentsch and Taylor 1999; Robinson and Berridge 2003; Bechara 2005; Everitt and Robbins 2005). As noted earlier, there is weak direct evidence for cognitive or self-control deficits in smokers (de Ruiter *et al.* 2009; Nestor *et al.* 2011). However, neuroplastic changes in the PFC of smokers have been observed (Brody *et al.* 2004; Kühn *et al.* 2010). Furthermore, the

association of nicotine addiction and impulsivity (Bickel *et al.* 1999; Mitchell 1999; Johnson *et al.* 2007; Bickel *et al.* 2008; Businelle *et al.* 2011; Peters *et al.* 2011; Peters and Büchel 2011) is suggestive of self-control deficiencies that may apply to non-drug rewards as well.

In a way, the results of study III can tell us something about the integrity of self-control functions in smokers. As noted earlier, self-control refers to the ability to inhibit actions, thoughts, or feelings that are either not relevant to the task at hand or are not desirable/detrimental (motor, cognitive, and affective inhibitory control) (Muraven and Baumeister 2000; Cohen and Lieberman 2010). Successful distancing from smoking CS relies in part on the ability to inhibit conditioned responses, that is feelings, to smoking CS. I could show that smokers can learn to use distancing to regulate cue-induced sexual arousal as well as craving for smoking in the lab, even in a state of overnight abstinence. Furthermore, degree of nicotine dependence did not alter the ability to regulate emotional responses to either cue class. Thus, interpreting ER as an indicator of affective inhibitory self-control, I conclude that I did not find evidence that smokers have an impaired self-control, neither in the context of smoking CS, nor in the context of reward cues. By contrast, the results indicate that smokers are able to exert affective self-control over craving when being placed in a safe environment and trained to use ER. Evidently, we cannot know from the present findings whether distancing would decrease craving or ultimately prevent smokers from smoking cigarettes in real life. But the results are more consistent with the idea that self-control functions in smokers are temporarily overridden by smoking CS and other internal cues (see next chapter) the moment cigarettes are available rather than that self-control functions of smokers are compromised in general (Bechara 2005).

5.3 Emotion regulation effects on neural smoking CS responses

I did not find evidence for greater smoking CS than neutral cue responses or craving correlations in the VST, which contradicts predictions of incentive incentive-sensitization theory (Robinson and Berridge 2003; Berridge 2007) and contrasts previous studies on smoking CS and craving (Due *et al.* 2002; David *et al.* 2005; Smolka *et al.* 2006; David 2007; Franklin *et al.* 2007; Wang *et al.* 2007; Kober *et al.*

2010; Stippekohl *et al.* 2010). On the one hand, the lack of observable VST signals could be owing to the experimental design—this did not allow an analysis of signal responses to individual pictures but only permitted an analysis of blocked responses over three pictures and a time window of 15 seconds. Such an analysis may be suboptimal to capture smoking CS responses, particularly in the NACC, where signals may be more short-lived, fluctuating, and varying with the degree of craving evoked by the individual pictures within one block (Walter *et al.* 2008). One solution to this problem could be to use slow event-related designs with single picture presentations and online ratings to map NACC activity more effectively. On the other hand, what I did observe was that smoking CS elicited neural activity in another part of the striatum, namely the caudate. Dorsal striatal (caudate and putamen) smoking CS signals in the absence of ventral striatal smoking CS responses have been previously reported (Janse Van Rensburg *et al.* 2008; McClernon *et al.* 2008; Janes *et al.* 2010). Such a dissociation concurs with the habit view that predicts a ventral to dorsal shift of drug CS-related activity over time (Everitt and Robbins 2005). Thus, the absence of smoking CS signals in the VST could be simply due to the fact that, in the current sample, cue responsivity had *already* shifted to the dorsal striatum. Such a shift would concur with the fact that smokers had already smoked for a very long time (average 13 years) when they participated in the experiment.

In the caudate, abstinent heavy smokers were not able to reduce smoking cue-induced signals via ER. A similar deficit could not be observed when heavy smokers were satiated or when they regulated erotic cues. Thus, the deficiency was abstinence- and drug-specific. Is it possible to interpret this finding in functional terms without making the mistake of doing reverse inference (Poldrack 2006)? By aligning interpretations with insights from drug addiction research and theory, one can draw conclusions as to what this deficit most presumably does as well as definitely does not reflect. First, the deficit is unlikely to signify an inability to regulate the subjective experience of craving for the following reasons: (a) heavy smokers reported that ER reduced their craving for smoking and (b) the respective caudate cluster did not correlate with craving or craving reductions to begin with. Second, as noted above, the habit theory predicts that the change from voluntary to compulsive, habitual drug use is accompanied by a ventral to dorsal shift of striatal cue activations (Everitt and Robbins

2005). According to this view, cue reactivity in the dorsal striatum reflects stimulus-response associations that trigger automatic drug consumption in the absence of conscious wanting or pleasure. Everitt and Robbins are not explicit about the exact location of such stimulus-response association representations. However, recent evidence from animal and human studies strongly suggests that the dorsolateral striatum (i.e., the putamen) is implicated in the habitual control of action whereas the dorsomedial striatum (i.e., the caudate) supports goal-directed action (Yin *et al.* 2004, 2006; Tricomi *et al.* 2009; Balleine and O'Doherty 2010). These findings corroborate a more refined theory on habit formation (Yin and Knowlton 2006) that posits that the ultimate turn from voluntary, pleasure-oriented to habitual, compulsive drug taking is caused not primarily by a ventral to dorsal striatal transfer, but by a shift from the goal-directed DLPFC-caudate to the sensorimotor SMA-putamen network. What does this tell us about the current caudate finding? If the Yin-Knowlton theory as well as current theories on caudate involvement in goal-directed action selection and learning (see chapter 1.1.2) were true, then caudate smoking CS responses in smokers rather indicate (cognitive) valuation than (automatic) habitual processes. In turn, heavy smokers' inability to downregulate such caudate signals during abstinence could suggest that their smoking behavior is still goal-directed (i.e., outcome-sensitive or pleasure-oriented), and that they are temporally and *partly* impaired in their ability to devaluate smoking cues. I would suppose this deficiency is partial, because I did not observe a similar negative correlation between FTND and VMPFC smoking signal reductions.

5.4 Emotion regulation interventions in the treatment of nicotine addiction

I once spoke to a nicotine addiction researcher at a conference where I presented preliminary results of the third study. He questioned my findings saying that "if smokers can learn to regulate craving so easily, why is it that they cannot use these skills in real life and quit smoking?". Though this statement certainly oversimplified certain aspects, it addressed an important point. Indeed, the present findings suggest that craving can be regulated very easily, in a sense very much easier than could have been expected, given the supposed role of smoking CS in nicotine addiction. If we asked

ourselves if the findings could be generalized, however, there would be some important limitations we would have to keep in mind: first, as noted earlier (see chapter 1.2.1), the cue exposure approach aims at allowing subjects to practice trained coping strategies in a very safe environment (Drummond *et al.* 1995; Drummond 2001; Barlow *et al.* 2004). To achieve craving reductions after one-time ER under such conditions does not imply that the effects will transfer to real life, where smoking CS are omnipresent and—most importantly—cigarettes *available*. To achieve sustainable effects, it would certainly require many training sessions as well as sufficient practice in the field. Second, in ER experiments, when measuring subjective emotion experience, ER researchers have to rely on verbal self-reports. Though participants are unlikely to deliberately forge these reports, their ratings are nonetheless subject to social desirability and self-fulfilling prophecy effects (Sudman and Bradburn 1974). Furthermore, retrospective ratings—as obtained in study III—are also susceptible to memory distortions. Consequently, ER effects on subjective ratings have to be interpreted with caution.

Third, nicotine addiction, like other addictive disorders, is a multifaceted disease. Many different factors contribute to the maintenance of nicotine addiction and to relapse, and cue-elicited craving is just one of them. In fact, the influence of negative affect (NA) and stress on maintenance and relapse has long been underestimated (Kenford *et al.* 2002; Carmody *et al.* 2007). Addicts even cite NA and social pressure as more important precipitants to relapse than cue-induced craving (Marlatt 1996). According to the negative reinforcement model (Baker *et al.* 2004), smoking can be understood as a strategy to escape NA. Indeed, it has been shown that smokers demonstrate deficient stress coping (i.e., they try to avoid NA) (Kassel *et al.* 2003), that smokers believe smoking helps them to cope with stress (Brandon and Baker 1991; Fucito *et al.* 2010), and that the presence of natural NA and stress coping resources predicts abstinence maintenance (Matheny and Weatherman 1998). Thus, NA and stress themselves can be viewed as internal cues that trigger urges to smoke because smoking will relieve NA. Consequently, a holistic approach to the treatment of nicotine addiction would have to address multiple factors that contribute to smoking. It suggests that cue exposure treatment *alone*—though suited to extinguish conditioned responses to smoking CS and to train the regulation of craving via ER—may not suffice to guarantee cessation: smokers would have to learn to better regulate NA and stressful life events as

well. This may take the form of ER training, the strengthening of distress tolerance (Brown *et al.* 2005), or the enhancement of mindfulness (awareness of what's distressing without being judgmental) (Vieten *et al.* 2010).

In the cognitive process theory of addiction (Tiffany 1990), very much like in the habit view (Everitt and Robbins 2005), it is assumed that smoking is essentially an automatic process (i.e., a habit). Over time, learning establishes rigid stimulus-response patterns that are triggered by external and internal cues such as smoking CS or NA and that will be ultimately carried out automatically, sometimes without conscious awareness. Only when the usual drug taking sequence is interrupted, for instance, by non-availability of the drug, cognitive craving comes into play. According to these theories, craving is not even a prerequisite for smoking behavior to occur. If smoking really was predominantly controlled by habits, it would follow that cognitive interventions should not primarily aim at the regulation of craving but at the disruption of automatic stimulus-response patterns. This can be achieved via trainings that target the sharpening of attention, enable smokers to become aware of established automatic patterns, and make them learn to deautomate behavior (Breslin *et al.* 2002).

In the light of the above remarks, it becomes evident that smoking cessation requires more than successful regulation of smoking CS-induced craving. For ER interventions during cue exposure, the examples suggest the following things: (a) Smokers should not only be exposed to smoking CS but to NA cues as well. Smokers could describe characteristic negative autobiographical experiences or stressful life events which are then presented to them in the form of written or auditory scripts while they apply ER (Kross *et al.* 2009) (b) Instead of simply aiming at distancing from possible cue-induced feelings upon CS and NA contact, ER interventions could encourage smokers first to become aware of what they are feeling in detail and then to regulate these very feelings (c) Given the role of NA in maintenance and relapse, ER instructions should never be formulated negatively, as in the Kober study (Kober *et al.* 2010). There, smokers were instructed to focus on the detrimental effects of smoking on health. Rather, smokers should be encouraged to use self-affirmative statements as supporting aids (e.g., "I can be a sporty, healthy and well-feeling person in two years if I manage to quit"). Such statements enhance self-efficacy expectations (Marlatt and Gordon 1985). Moreover, positive future tagging as operationalized in the above

example has been shown to reduce impulsivity in healthy controls (Peters and Buchel 2010)

6. Conclusions

The results of this dissertation contribute to the literature on emotion regulation and nicotine addiction by demonstrating that

- Emotion regulation can diminish feelings of reward anticipation and pleasure in the conext of monetary reward.
- Emotion regulation not only attenuates neural signals during the expectation of reward, but also alters encoding of neural reward prediction errors during the evaluation of reward.
- Emotion regulation can reduce the motivation to obtain reward. The putamen is one brain region where motivation is converted into action.
- Successful regulation of neural reward expectation is partly mediated by DLPFC modulation of putamen reward responses.

- Smokers can learn to regulate craving for smoking as well as neural smoking cue responses in addiction-relevant brain regions, even in a state of overnight nicotine abstinence.
- Degree of nicotine dependence does not alter the ability to regulate craving via emotion regulation.
- Prolonged nicotine abstinence induces a temporary state in which heavy smokers cannot readily use shortly-trained emotion regulation skills to regulate smoking cue responses in the caudate.
- Emotion regulation interventions in nicotine addiction should train the regulation of both craving and negative affect.

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