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Neurobiological Correlates of Pathological Gambling: Temporo-Spatial Evidence Derived from fMRI and EEG Studies

Dissertation
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Preface

The neuronal activity of risk-assessment/decision making or reward processing in pathological gambling has been mostly studied within paradigms of low ecological validity. Results have demonstrated that pathological gamblers suffer from a generally lowered sensitivity to perceived risks and rewards when tested in a gambling-unrelated environment. On the other hand results in addiction research have shown that addicted persons demonstrate an enhancement of neuronal activity in the same brain regions in situations related to their addiction, named cue-reactivity. The aim of this study was to compare pathological gamblers with occasional gamblers in an environment rich in gambling cues with a high ecological validity. It is proposed that the environment of the chosen quasi-realistic blackjack game should enhance neuronal brain network activity in PG similar to the cue-reactivity studies in addiction research. Furthermore, the design used here allows for a differential testing of those effects both within situations of risk assessment and reward processing.

The two experimental studies presented in this thesis were accomplished within the framework of a dissertation project at the University of Bremen, supported by a research grant (11/174/05) of the Bremen University Research Commission to Prof. Dr. G. Meyer and Prof. Dr. Dr. M. Herrmann. All studies were conducted at the Department of Neuropsychology and Behavioral Neurobiology (Prof. Dr. Dr. M. Herrmann).

Abstract

Experiment 1

In the first study functional magnetic resonance imaging (fMRI) data in occasional gamblers (OG) and pathological gamblers (PG) were obtained during a quasi-realistic blackjack game. The present experiment focused on neuronal correlates of risk assessment and reward processing.

Participants had to decide whether to draw or not to draw a card in a high-risk or low-risk blackjack situation. It was assumed, that PG would show differences in prefrontal and ventral striatal brain regions in comparison to OG during risk assessment and as a consequence of winning or losing money. Although both groups did not differ with respect to behavioral data, blood oxygen level dependent (BOLD) signals in PG and OG significantly differed in thalamic, inferior frontal, and superior temporal regions. Whereas PG demonstrated a consistent signal increase during high-risk situations and a decrease in low-risk situations, OG presented the opposite pattern.

During reward processing as derived from contrasting winning vs. losing situations, both PG and OG groups showed an enhancement of ventral striatal and posterior cingulate activity. Furthermore, PG demonstrated a distinct fronto-parietal activation pattern which has been discussed to reflect a cue-induced addiction memory network triggered by gambling-related cues.

Experiment 2

The second experiment investigated event-related potentials (ERPs) in occasional gamblers (OG) and pathological gamblers (PG) during a quasi-realistic blackjack scenario to examine regional source (RS) models of risk assessment and reward processing based on fMRI activation patterns from experiment 1. Participants had to decide whether (to draw) or not to draw a card in a high-risk or low-risk blackjack situation.

Although both groups did not differ in behavioral data, ERP signals in PG and OG significantly differed in P3b and late positive potential (LPP) amplitudes on high-risk vs. low-risk decisions. An fMRI constrained RS model during risk assessment yielded larger source moments in PG in the high-risk vs. low-risk comparison during early time windows in frontal and temporal brain regions, followed by thalamic, frontal, and temporal activations within later time windows.

During reward processing, as derived from contrasting winning vs. losing situations, PG demonstrated enhanced fronto-central N1 amplitude and centro-parietal differences in the P3b time window. There were larger source moments in PG during early time windows in fronto-central and parietal networks, followed by middle frontal source activity in the 400-450 ms (millisecond) time window.

Pathological gambling (PGG) is suggested to be reflected by early risk-related frontal and temporal modulations, which became not significant in ERPs, followed by enhanced P3b amplitude, probably associated with intensified evaluation processing or context updating in high-risk decisions. LPP enhancement in high-risk decisions in PG might represent stronger cue-related craving or arousal, potentially triggered by thalamic, frontal, and temporal generators. Early N1 enhancement in PG during win trials might reflect early attentional processing, probably generated in anterior cingulate cortex. Later valence-related P3b modulations in PG point to increased context updating with underlying frontal sources.

To conclude, high-risk as well as win situations might serve as cues in PG reflected in stronger activations in arousal-related brain networks.

Keywords: pathological gambling, risk assessment, reward processing fMRI, EEG, source analysis

German Abstract/Deutsche Zusammenfassung

Experiment 1

In Studie 1 wurden fMRI Daten von Gelegenheitsspielern (OG) und pathologischen Spielern (PG) während eines quasi-realistischen Black Jack-Spiels erhoben. Das Experiment konzentrierte sich auf die neuronalen Korrelate von Risikobewertung/Entscheidungsfindung und Belohnungsverarbeitung. Die Teilnehmer des Experiments mussten sich während einer hoch- oder niedrigriskanten Black Jack Situation entscheiden, ob sie eine weitere Karte kaufen wollten.

Die Annahme war, dass PG und OG Unterschiede in Aktivierungsmustern in präfrontalen und ventro-striatalen Hirnregionen während der Risikobewertung und aufgrund des Gewinnens oder Verlierens von Geld aufweisen. Obwohl sich beide Gruppen bezüglich ihrer Verhaltensdaten nicht voneinander unterschieden, zeigte das BOLD Signal im Gruppenvergleich (PG vs. OG) signifikante Unterschiede in thalamischen, inferior frontalen und superior temporalen Gebieten. Während PG in der hochriskanten Bedingung einen Signalanstieg und in der niedrigriskanten Bedingung einen Signalabfall erkennen ließen, war bei den OG ein umgekehrtes Muster in den Signalverläufen zu beobachten.

Bei der Belohnungsverarbeitung, abgeleitet aus dem Kontrast Gewinn vs. Verlust, manifestierte sich in PG und OG ein Anstieg der Aktivierung im ventralen Striatum und posterioren Cingulum. Außerdem war im Gruppenvergleich (PG vs. OG) ein fronto-parietales Netzwerk aktiv, welches mit dem von Glücksspiel-spezifischen Reizen induzierten Suchtgedächtnis in Verbindung gebracht wird.

Experiment 2

In Experiment 2 wurden ereigniskorrelierte Potentiale (EKP) von OG und PG während eines quasi-realistischen Black Jack Spiels aufgenommen (das Design entspricht dem aus Experiment 1). Ziel war es, regionale Quellenmodelle der Risikobewertung/Entscheidungsfindung und der Belohnungsverarbeitung basierend auf den fMRI Aktivierungen aus Experiment 1 zu erhalten. Die Teilnehmer von Experiment 2 mussten sich, wie in Experiment 1, während einer hoch- oder niedrigriskanten Black Jack Situation entscheiden, ob sie eine weitere Karte kaufen wollten. Beide Gruppen zeigten keine Unterschiede in ihren Verhaltensdaten, dennoch unterschieden sich PG und OG

signifikant in der P3b und LPP Amplitude im Vergleich zwischen der hochriskanten mit der niedrigriskanten Bedingung.
Das regionale Quellenmodell der Risikobewertung/Entscheidungsfindung offenbarte höhere frontale und temporale Quellenaktivität bei PG in frühen Zeitfenstern, gefolgt von thalamischen, frontalen und temporalen Quellen in späteren Zeitfenstern.
Während der Belohnungsverarbeitung, abgeleitet vom Kontrast Gewinn- vs. Verlustsituation, zeigten PG eine erhöhte fronto-zentrale N1 Amplitude und zentro-parietale Unterschiede im P3b Zeitfenster. Die Quellenaktivität der PG während frühen Zeitfenstern war höher als in OG in fronto-zentralen und parietalen Netzwerken, gefolgt von medio-frontaler Aktivität im 400-450 ms Zeitfenster.
Es wurde angenommen, dass pathologisches Spielverhalten mit frühen risikoabhängigen frontalen und temporalen Veränderungen einherging, welche in den EKP keine signifikanten Gruppenunterschiede zeigten. Darauf folgte eine erhöhte P3b Amplitude von PG, die wahrscheinlich eine verstärkte Kontextaktualisierung oder Evaluation, speziell bei hochriskanten Entscheidungen, widerspiegelt. Der LPP-Erhöhung während hochriskanter Bedingungen in PG könnte ein stärkeres reizinduziertes Verlangen oder Erregung zugrunde liegen, das potentiell von thalamischen, frontalen und temporalen Quellen ausgelöst wurde. Die frühe N1-Erhöhung in PG während Gewinnsituationen könnte auf eine frühe Aufmerksamkeitsmodulierung mit Generatoraktivität im anterioren Cingulum (ACC) hindeuten. Die spätere, an die Valenz gekoppelte, P3b Modulation in PG steht möglicherweise mit stärkerer Kontextaktualisierung in den für Erregung zuständigen Hirnarealen in Zusammenhang.

Schlagworte: Pathologisches Glücksspiel, Risikobewertung/Entscheidungsfindung, Belohnungsverarbeitung, fMRI, EEG, Quellenanalyse

List of Abbreviations

5-HT	5-hydroxytryptamine, serotonin
ACC	anterior cingulate cortex
ACTH	adrenocorticotropic hormone
ADHD	attention deficit hyperactivity disorder
BA	Brodmann area
BOLD	blood oxygen level dependent
COMT	catechol-O-methyltransferase
CRF	corticotropin-releasing factor
CRH	corticotropin-releasing hormone
DA	dopamine
DLPFC	dorsolateral prefrontal cortex
DRD1	dopamine-D1-receptor
DRD2	dopamine-D2-receptor
DSM	diagnostic and statistical manual of mental disorders
EEG	electroencephalogramm
EKP	ereigniskorrelierte Potentiale
ERN	error-related negativity
ERP(s)	event-related potential(s)
fMRI	functional magnetic resonance imaging
FRN	feedback-related negativity
FSP	frontal selection positivity
GABA	gamma-aminobutyric acid
GFP	global field power
HPA	hypothalamic-pituitary-adrenal
ICD	international classification of disorders
IFG	inferior frontal gyrus
IGT	Iowa gambling task
KFG	Kurzfragebogen zum Glücksspielverhalten
LC	locus coeruleus
MAO	monoamine oxidase
m-CPP	meta-chlorophenylpiperazine
mRNA	messenger ribonucleic acid

ms	milliseconds
MTG	middle temporal gyrus
NAc	nucleus accumbens
NE	norepinephrine
OFC	orbitofrontal cortex
OFG	orbitofrontal gyrus
OG	occasional gamblers
PFC	prefrontal cortex
PG	pathological gamblers
PGG	pathological gambling
POMC	proopiomelanocortin
PVN	paraventricular nucleus
PTSD	posttraumatic stress disorder
RDS	reward deficiency syndrome
RS	regional source(s)
RT	response time(s)
SFG	superior frontal gyrus
SOGS	South Oaks gambling screen
STG	superior temporal gyrus
VMPFC	ventromedial prefrontal cortex
VTA	ventral tegmental area

1 General Introduction

The present thesis examines the neuronal correlates of risk assessment and reward processing in pathological gamblers (PG) compared to occasional gamblers (OG). By combining functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) data, the present dissertation aims at providing insight into the spatio-temporal characteristics underlying pathological gambling (PGG) behavior.

The first chapter introduces PGG and theories of PGG, followed by an overview of disorders of different neurotransmission systems involved in PGG and genetic influences on PGG. Furthermore, addiction and cue-induced changes in the perception-action cycle and the somatic marker hypothesis are emphasized. At the end of this chapter, aims and the scope of the present thesis are provided.

1.1 What is pathological gambling? - Theories

Gambling means to stake something of value at risk, while hoping or expecting to get back something of higher value. PGG is classified as an “impulse control disorder not elsewhere categorized” in the Diagnostic and statistical manual (DSM). In the International Classification of Disorders (ICD), PGG is classified under “habit and impulse disorders” as well as pyromania, kleptomania and trichotillomania (Potenza, 2008). PGG share core components of an addiction, like (a) recurrent engagement in a behavior in spite of negative consequences, (b) weakened self-control related to the engagement in that behavior, (c) recurrent compulsion in that activity, and (d) urge or craving before the engagement in that activity, as well as tolerance and withdrawal (Potenza, 2006). Therefore, PGG as a behavioral addiction might function as a model to unravel the underlying mechanisms in drug addiction, because there is no influence of substances on a physiological level.

Evidence for temporal dynamics with respect to gambling severity came from Meyer (2005), who described different phases in the development of PGG. PG of self-help groups reported that the phase of occasional gambling lasted on average 2.5 years, followed by a 5.5 years phase of intensive gambling. It was reported, that after 3.5 years gambling PG or their partners experienced the gambling behavior as problematically. Looking closer to the development and maintenance of PGG, biological, psychological and social factors might be responsible for the development and maintenance of PGG in an interactive way (Sharpe,

2002). In a pathways model of problem gambling and PGG Blaszczynski & Nower (2002) proposed three paths in the development of gambling problems: first, a pathway of behavioral conditioning, which has influence on reward pathways of the brain; second, a path of social life circumstances, emotional problems, and biological vulnerabilities as mediators. In a third pathway impulsive psychopathology like attention deficit hyperactivity disorder (ADHD) and dopaminergic abnormalities is supposed to play a crucial role in the development of PGG. The pathways model is aimed to help clinicians in identifying and disentangling distinct subgroups of PGG needing specific treatment approaches.

Volkow et al. (2003) introduced a model of an addicted brain with memory holding an important function (Figure 1.1). The authors suggested that context and previous experience influence memory regarding the saliency of a stimulus since it is assumed that memories are stored as associations of positive and negative experience elicited by a stimulus.

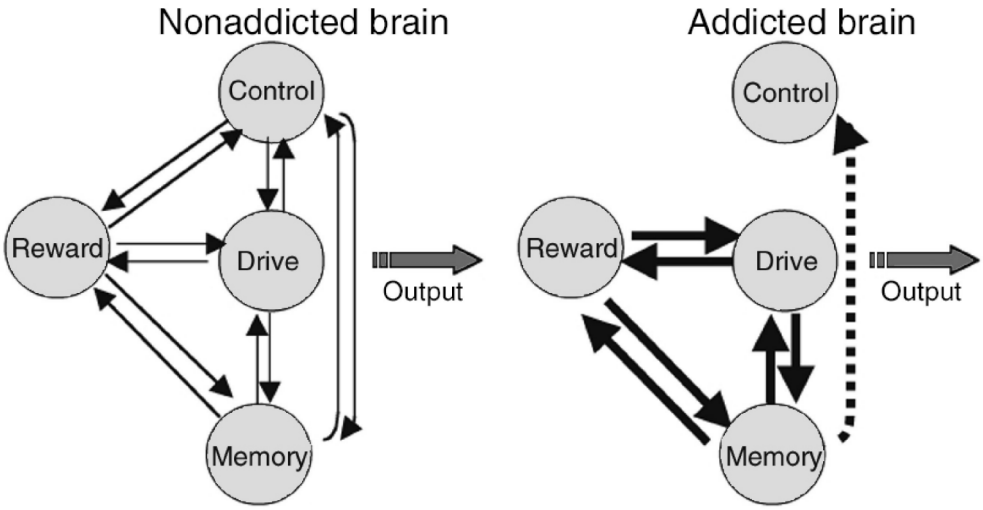

Figure 1.1 Network model of a non-addicted brain (left) and addicted brain (right); (Figure adapted from Volkow et al., 2003).

According to the model the authors expect that addicted persons are characterized by an enhanced reward value and memory related to their preferred addiction, resulting in an uncontrolled compulsive behavior. Therefore, the system in the addicted brain is thought to be strengthened via bidirectional connections within the “memory-reward-drive network" (see bold arrows in Figure 1.1 right) which in turn leads to a loss of cognitive control driven by addiction memory. This is in accordance with results of PG, demonstrating a

hypersensitivity to gambling cues (Tanabe et al., 2007), possibly caused by priming of gambling constructs in memory (McCusker & Gettings, 1997).
Summarizing, PGG seems to be a heterogeneous impulse control disorder, sharing core components of an addiction, where social, biological, and memory-related factors might play a crucial role in its development and maintenance.

1.2 Disorders of neurotransmission systems involved in pathological gambling

The following chapters deal with disorders in neurotransmission systems involved in PGG, starting with the dopaminergic reward system, followed by a description of the serotonergic and norepinephrinergic system. Finally, the opioid and endorphin systems are introduced in relation to PGG.

1.2.1 Dopaminergic reward system

According to the sensitization hypothesis repeated administration of drugs sensibilizes the dopamine (DA) system to the specific drug and associated drug cues (Robinson & Berridge, 1993). This hypothesis was developed based upon the observation that periodic, recurrent application of electrical stimuli to limbic brain areas creates a gradual sensitive neuronal locus. As a consequence, the sensitive locus shows a continuous, strengthened sensitivity to a consecutive administration of that specific stimulus or related cues of that stimulus (Adinoff, 2004).
Another evidence for the important role of DA in addiction came from Dackis and Gold (1985), who introduced the DA depletion hypothesis of addiction. It is based on the finding, that pleasurable feelings of cocaine use are related to acute stimulation of mesolimbic DA systems. The key point is that chronic cocaine use is thought to cause overstimulation of DA neurons and excessive synaptic DA metabolism, which in turn leads to DA depletion. As a consequence, the DA deficit is hypothesized to result in a craving to refill depleted DA stores.
The mesolimbic pathway was identified as the important component in the processing of reward since natural rewards (sex, food) (Kelley & Berridge, 2002) just like substances (alcohol, caffeine, cocaine, marijuana, nicotine, amphetamine, and opiates) (Due et al., 2002; Kalivas & Volkow, 2005) increase extracellular mesolimbic DA concentrations. This path arises from dopaminergic cell bodies in the ventral tegmental area (VTA), a

nucleus located in the ventral midbrain close to the substantia nigra. These dopaminergic axons project to the nucleus accumbens (NAc), amygdala, bed nucleus of stria terminalis, lateral septum, and lateral hypothalamus. A second mesostriatal pathway projecting from the substantia nigra to the dorsal striatum modulates motor activity (Adinoff, 2004). The author concluded that the mesolimbic system assesses the salience or the value of a potential reinforcer via DA signaling to promote goal-directed behaviors. Furthermore, the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) are innervated from the VTA via the mesocortical pathway. Interestingly, the NAc is connected to the OFC, ACC, insula, and hippocampus with glutaminergic and other mutual neurotransmitter connections.

As to gambling behavior DA agonists, like amphetamine, induced higher motivation to gamble and higher reading speed of gambling-related words vs. neutral words in problem gamblers (Zack & Poulos, 2004). In addition, an overstimulation of mesolimbic DA receptors due to Levodopa (precursor to dopamine) therapy led to problematical gambling behavior of Parkinson patients (Gschwandtner et al., 2001; Molina et al., 2000).

Volkow et al. (2004) argued that cue-related stimuli in the environment are high in salience and, therefore, stimulate DA cells. Due to overstimulation of DA cells through salient drug-related cues activation thresholds of active DA cells after perceiving drug-unrelated cues in the environment are disrupted. This means that an addicted person needs a higher amount or level of natural cues to activate DA cells. Moreover, the sensitivity to drug-unrelated cues is reflected by a reduction of DA release and DA receptors in the striatum. The authors differentiated DA circuits, concerning to their functional involvement in addiction. The mesolimbic circuit which includes the NAc and hippocampus is important for the reward linked to the drug, memories related to the drug, and conditioned behavior. In addition, the mesocortical circuit, with the core components cingulate gyrus and orbitofrontal gyrus (OFG), is suggested to play a crucial role in compulsive drug intake and inhibitory problems. Moreover, the nigrostriatal circuits, with the ventral striatum as its core component, are thought to be responsible for habit generation. Furthermore, Volkow and colleagues (2004) described the role of the OFC in addiction in more detail. First, the region is expected to be involved in the processing of the reinforcement characteristics of a stimulus in relation to a competing alternative stimulus. Second, the OFC is associated with the processing of motivation and drive. Third, the region plays a crucial role in the acquisition of stimulus-reinforcement coupling in conditioned behavior. Fourth, it is part of a pathway responsible for the inhibitory control of emotional responses.

Fifth, dysfunction of the OFC is related with the occurrence of compulsive behavior (Everitt & Robbins, 2005; Everitt & Wolf, 2002).

As a consequence, Volkow et al. (2004) proposed some therapeutic implications for the treatment of addiction. The reward value of a drug should be decreased, whereas the value of alternative non-drug-related reinforcers should be strengthened. Additionally, the learned positive associations to drug and drug-cues have to be attenuated. As a further crucial suggestion the control should be enhanced in the frontal cortex, where the ACC is expected to play an important role in the inhibition of compulsive responses.

Wolfram Schulz (2000) further described natural reward systems and their possible involvement in drug addiction. The research of his group mainly focused on non-human primates, nevertheless, their results provide a framework for better understanding addictive behavior in humans. An important concept was introduced, called reward prediction error, which is defined as the discrepancy between the occurrence of a reward for showing a specific action and the predicted occurrence of reward following that action. The prediction error is positive when the reward after a specific action was unpredictable - as a result of this sequence the particular action becomes associated with its consequences/reward. When the consequences of the action are learned, the prediction error drops to zero, which means, the reward is fully predictable. On the other hand, when an expected reward is not obtained following an associated action, the prediction error becomes negative and as a consequence behavior is eliminated. In experiments with monkeys Hollerman and Schulz (1998) linked phasic DA response in the pars compacta of substantia nigra and the medially adjoining VTA directly to the reward prediction error. Monkeys had to release a resting key to obtain an invisible food response. After they had learned that a stimulus predicted a reward at a specific time point, the phasic DA response was higher following surprising rewards, unchanged after predicted rewards, and depressed after an expected reward was not delivered. Tremblay & Schulz (1999) showed that the striatum and the OFC were related to the expectation of reward. As neurons in the OFC demonstrated higher activity when a preferred reward was expected rather than a non-preferred, it was concluded that neurons in that region are sensitive to the relative motivational value of a reward. Consequently, the OFC seems to be involved in the processing of the subjective importance of a stimulus. Especially in a gambling-related environment PG might demonstrate differences compared to healthy persons concerning stimulus processing as the sensitivity of PG for gambling cues could enhance the relative motivational value of specific situations.

Koob & Le Moal (2008) argued that a DA function decrease coupled with a corticotropin-releasing factor (CRF) function increase plays a crucial role in the development and maintenance of compulsive drug use.

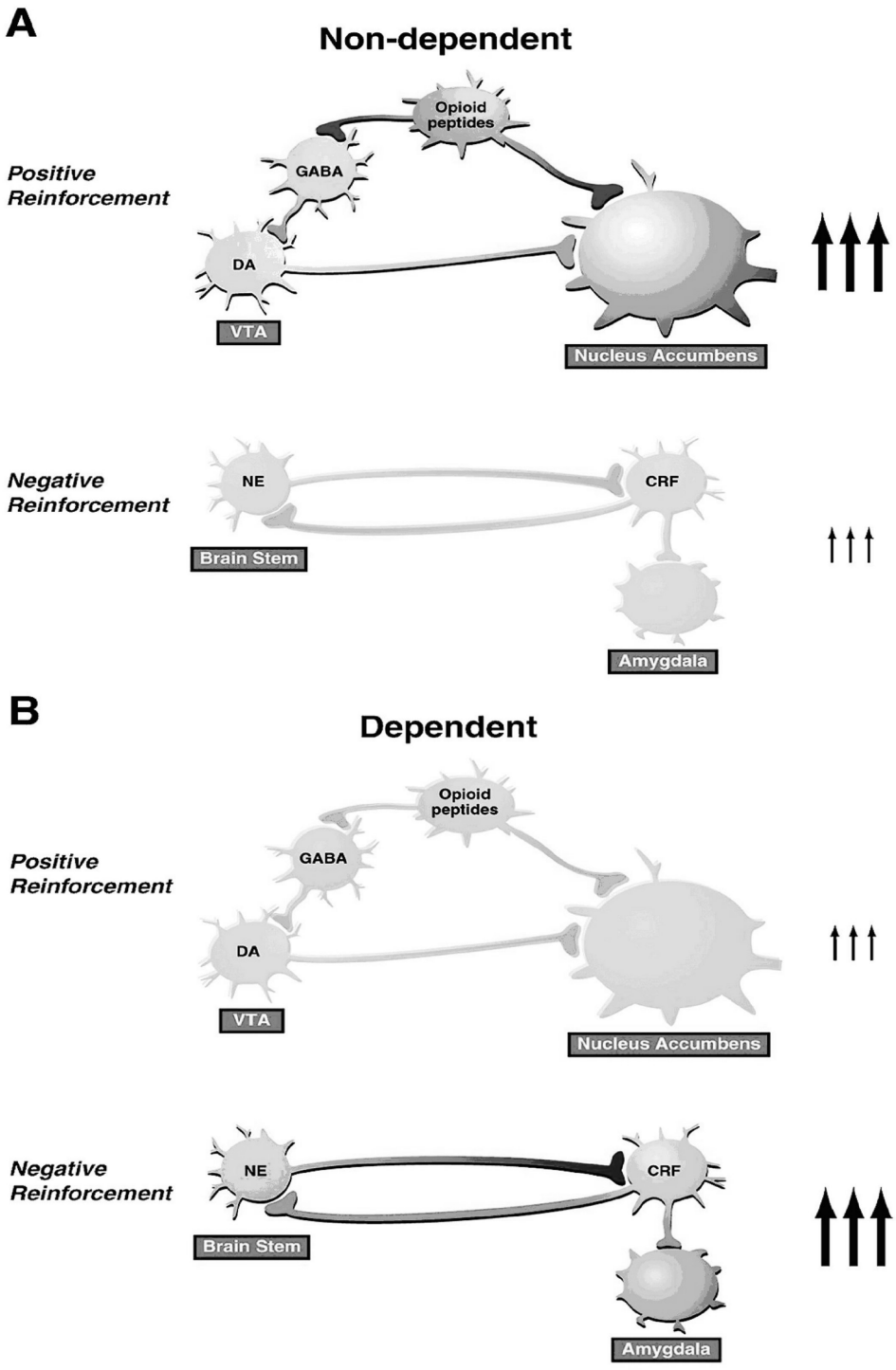

Figure 1.2 Neurocircuitry in the transition from (A) non-dependent drug taking to (B) dependent drug taking (Figure adapted from Koob & Le Moal, 2008; GABA = gamma-aminobutyric acid; DA = dopamine; NE = norepinephrine; CRF = corticotropin-releasing factor; VTA = ventral tegmental area).

The authors related addiction to decreased reward processing, coupled with an enhancement of so-called antireward systems, which in turn lead to compulsive drug use. The antireward system activity was argued to be a consequence of excessive activation of the reward system (see also Figure 1.2). It is assumed that the antireward system is a brain system sensitive to stress with both decreased DA and opioid peptide function and increased CRF function. In response to stress corticotropin-releasing hormone (CRH) is secreted by the paraventricular nucleus of the hypothalamus. CRH stimulates corticotropes in the pituitary gland to secrete adrenocorticotropic hormone (ACTH) in the HPA (hypothalamic-pituitary-adrenal) axis, a major part of the neuroendocrine system that controls reactions to stress. ACTH in turn stimulates the adrenal glands to release epinephrine to prepare a fight or flight response. Koob & Le Moal (2008) proposed that non-drug addictions, like PGG share core characteristics of impulsivity and compulsivity observed in drug addiction.

Altogether, the interplay of the mesocortical and mesolimbic dopaminergic pathways might be good candidates for studying PGG behavior in the sense that they influence goal-directed behavior via salience of a reinforcer and its subjective importance.

1.2.2 Serotonergic system

Serotonin (5-hydroxytryptamine or 5-HT) is released in the neurons of the raphe nuclei in the brainstem, where the axons innervate large areas of the central nervous system. Additionally, 5-HT activity was reported to be closely connected with behavioral inhibition, emotional stabilization, appetite modulation, sensory reactivity, pain sensitivity, sleep, sexual behavior, and cognitive function (Goodman, 2008).

Pallanti et al. (2006) demonstrated that postsynaptic serotonergic receptor stimulation elicited an enhanced prolactin response in PG when compared to controls, which was interpreted to reflect a hypersensitivity of the postsynaptic serotonergic function. It was reported that the feeling of being ‘‘high’’ after partial 5-HT agonist meta-chlorophenylpiperazine (m-CPP) stimulation in PG was comparable to perceived sensations during gambling, analogous to alcoholic subjects’ reports that their m-CPP-induced experience was similar to their experience with ethanol (Buydens-Branchey et al., 1997). Additionally, the authors concluded that enhanced sensitivity to 5-HT stimulation could be a factor of susceptibility for addiction in behavioral and substance addictions. Hollander et al. (2000), however, reported a reduction of urge to gamble in PG after

selective 5-HT reuptake inhibitor fluvoxamine treatment, which is in line with Nordin & Eklundh (1999), who observed a deficit of 5-HT in PG, which might be related to impulsive behavior expressed by PG. Contrary to the reported serotonergic deficit associated with diminished impulse control in PG, Perez de Castro (1999) observed less polymorphism at a 5-HT transporter gene more frequently in PG than in controls (see also chapter 1.3 second paragraph) pointing to an enhanced level of 5-HT in PG.

To conclude, alterations within the serotonergic system and an increased sensitivity to 5-HT stimulation point to a general distortion of the 5-HT system in PG, which might be involved in the expressed decrease of impulse control and inhibition in this group.

1.2.3 Norepinephrinergic system

Norepinephrine (NE) is released as a physiological reaction to a stressful event and is produced primarily by the locus coeruleus (LC) in the brain stem (Koob, 2009). Additionally, NE is synthesized from DA by the enzyme DA beta hydroxylase. The norepinephrinergic system in the brain has two main ascending projections: the dorsal norepinephrinergic bundle, originating in the LC and projecting to the hippocampus, cerebellum, and forebrain; and the ventral norepinephrinergic bundle, projecting from the pons and medulla to the hypothalamus, midbrain, and extended amygdala (Moore & Bloom, 1979). Goodman (2008) speculated that a crucial factor in the relationship between the norepinephrinergic system and addiction might be an increased level of extracellular NE and its effects on the dopaminergic system. Furthermore, the author reported that stress is the most prevalent correlate of increased levels of extracellular NE. As a reaction to acute stress NE drives CRF release which is associated with increased activity in the nucleus tractus solitarius, the LC, and the dorsal medulla. Consequently, during a stressful event the NE-system inhibits the prefrontal cortex (PFC), pushing the brain in alarm condition to survive life-threatening situations through instinctual responses, while inhibiting complex behavior (Gold & Chrousos, 2002). Concerning PGG, a study of Meyer et al. (2004) demonstrated enhanced NE levels in PG compared to controls during casino blackjack gambling, which was interpreted as generally higher levels of expectancy and enhanced urge to gamble.

Consequently, the norepinephrinergic system might be important for the development and perpetuation of PGG, especially for disinhibition during gambling (DeCaria et al., 1998).

1.2.4 Opioidsystem / endorphinsystem

Oswald & Wand (2004) described three groups of endogenous opioid peptides, which are derived from a specific precursor hormone: first, the endorphins from the β-endorphin/ACTH precursor proopiomelanocortin (POMC); second, the dynorphins and neoendorphins from the precursor prodynorphin; and third, the enkephalins from the precursor proenkephalin. The precursor hormones originate from distinct genes and separate messenger ribonucleic acid (mRNA). In their function as neuromodulators or neurotransmitters the opioid peptides influence psychomotor stimulation, positive reinforcement, adaptive processes, drinking and eating, sexual behaviors, pituitary function, thermoregulation, nociception, and mood (Oswald & Wand, 2004). Posttranslational processing of POMC generates β-endorphin and ACTH. Neurons generating β-endorphin in the brain are situated mainly in the ventromedial arcuate nucleus of the hypothalamus, which innervates far-reaching brain structures comprising many parts of the hypothalamus and the limbic system. POMC synthesis includes the nucleus tractus solitarius, which is important for relieving pain, and the pituitary gland, comprising the highest concentration of POMC mRNA in the body. Proenkephalin is produced in many regions of the brain, whereas POMC synthesis is limited to specific regions. The striatum, the ventral medial nucleus of the hypothalamus, and the dentate gyrus of the hippocampus contain the highest density of proenkephalin mRNA (Oswald & Wand, 2004). Interestingly, β-endorphin and enkephalin peptides increase DA release within the NAc through their interactions with opioid receptors, hence playing a crucial role in reward processing (Koob, 1992). In this sense addiction is thought to be a consequence of abnormal synaptic plasticity due to inappropriate DA release by exogenous opioids (Nestler & Aghajanian, 1997).

As a consequence of stress, CRH neurons in the paraventricular nucleus (PVN) of the hypothalamus receive convergent input from various major neurotransmitter systems that support the dynamic regulation of the HPA axis. Stimulatory signals from serotonergic and norepinephrinergic neurons and also inhibitory signals from gamma-aminobutyric acid (GABA)- and β-endorphin-releasing neurons contribute to this regulatory input (Calogero, 1995). Valentino & Van Bockstaele (2001) concluded that stress-induced opioid neurotransmission may play a role in antagonizing potentially harmful effects of ongoing stress by calming down the HPA axis stress activity. Oswald & Wand (2004) hypothesized, that a lesion in opioid neurotransmission should impede both stress-regulation and reward processing, because β-endorphin neurons in the arcuate nucleus of

the hypothalamus influence the inhibition of CRH release in the PVN of the hypothalamus and enhancement of DA release in the NAc.

Referring to PGG, Shinohara et al. (1999) analyzed blood samples of Japanese Pachinko (slot machine) players. Before playing Pachinko, beta-endorphin secretion increased significantly. The number of hours subjects play Pachinko in a week and the differences in beta-endorphin between start of a winning streak and baseline were positively correlated. Because of this finding, the authors concluded that beta-endorphin may be involved in habit formation in Pachinko players. Meyer et al. (2004), however, showed no differences in beta-endorphin levels of problem gamblers as a reaction to placing the bet (real money) in a casino blackjack game compared to a control situation (playing only for points at the laboratory). Grant et. al. (2006) speculated that the efficacy of opioid antagonists in addiction treatment pertains to opioidergic modulation of the mesolimbic DA network. This was demonstrated when subjects, assigned to the opioid antagonist nalmefene showed statistically significant reductions in gambling urges and PGG behavior (Grant et al., 2006). The authors concluded that opioid antagonist medication leads to a lowered urge to engage in addictive behavior and longer periods of abstinence, which is compatible with an underlying ventro-striatal dopaminergic mechanism of action (Kelly et al., 2009).

To summarize, the opioidsystem involved in the release of DA and the reduction of stress seems to be connected to the reported feelings of euphoria in PG (Legg England & Gotestam, 1991) and strengthening of the engagement in addictive behavior. This is confirmed by the fact that opioid antagonists have been shown to be effective in the treatment of PG (Grant et al., 2008; Grant et al., 2006; Kim et al., 2001). Consequently, alterations in interacting neurotransmission systems seem to play a crucial role in the development and maintenance of PGG.

1.3 Genetics and pathological gambling

Eisen et al. (1998) examined the contribution of inherited factors and experiences shared by twin siblings during childhood to the vulnerability to PGG. Data was collected via the Diagnostic Interview Schedule Version III-Revised (Eisen et al., 1987). Participants were 6718 members of the nationally distributed Vietnam Era Twin Registry of male-male monozygotic and dizygotic twin pairs who served in the military during the Vietnam era. Inherited factors explained between 35% and 54% of the liability for the five individual symptoms of PGG behavior. Furthermore, familial factors explained 62% of the diagnosis of PGG disorder. The authors concluded that familial factors have an important influence

on risk for PGG behavior. In addition, increasing access to legalized gambling among persons, being vulnerable because of familial factors might lead to a higher prevalence of PGG. Slutske et al. (2000) studied adult male twin pairs from the Vietnam Era Twin Registry. They applied genetic model-fitting technique to quantify the extent to which the risk for alcohol dependence could explain the genetic and environmental risk for PGG. The risk for alcohol dependence accounted for 12-20% of the genetic variation and 3-8% of the non-shared environmental variation in the risk for PGG. The authors concluded that risk for alcohol dependence accounts for a significant but modest proportion of the genetic and environmental risk for PGG.

The low-activity 3-repeat allele of the 30-bp monoamine oxidase (MAO)-A promoter polymorphism, which is related to lower transcriptional and lower enzymatic activity, was significantly increased in male PG compared to controls (Ibáñez et al., 2000; Perez de Castro et al., 1999, 2002). Furthermore, Perez de Castro et al. (1999) showed that the less functional short variant of a polymorphism at the 5-HT transporter gene (5-HTTLPR), related to decreased promoter activity, was observed more frequently in PG than in controls. This finding proved to be exclusively true for males. The fact that 5-HT, NE, and epinephrine are mainly broken down by MAO-A, creates evidence for a serotonergic dysfunction in PG. Moreover, the A1 allele of the human dopamine-D2-receptor (DRD2) gene has been shown to be significantly more often present in persons with addictive disorders (drug addiction, some forms of severe alcoholism) and other impulsive behaviors, than in healthy persons. In a group of PG 50.9% carried the D2A1 allele versus 25.9% of the controls (Comings et al., 1996). In PG with pronounced gambling behavior the percentage increased to 63.8. These results suggest that genetic variants at the DRD2 gene play a specific role in PGG and support the view that the presence of variants of this gene are a risk factor for the development of impulsive and addictive behaviors. Comings et al. (1997) tested the hypothesis that the dopamine-D1-receptor (DRD1) gene might play a role in addictive behaviors. They examined the alleles of the DRD1 Dde I polymorphism in three independent groups of subjects with different types of compulsive, addictive behaviors, like Tourette syndrome, smoking, and PGG. In all three groups they observed a significant increase of the frequency of homozygosity for the DRD1 Dde I 1 or 2 alleles in subjects in connection with the severity of addictive behaviors. In addition, the DRD1 11 or 22 genotype was significantly more often present in PG than in control participants. These results provide evidence for an important role of genetic variants of the DRD1 gene in addiction and PGG. A study by Comings et al. (2001) demonstrated that 5-HT, DA, and

NE genes contributed approximately equally to the risk for PGG. Additionally, the authors showed that genes, affecting different brain functions, play an additive role as risk factors for PGG. The reported results point to a polygenetic inheritance of specific traits, which is in accordance with Comings (1998), who revealed that single genes only explain a low percentage (1% to 5%) of variance. Chen et al. (2005) linked pathological aggression in adolescents, a complex behavioral disorder, to polymorphisms of the dopaminergic system. They concluded that underlying mechanisms of pathological aggressive behavior partly resemble mechanisms of other forms of impulsive behaviors like PGG. Additionally, both the DRD2 gene and the DA transporter gene DAT1 polymorphisms showed a positive correlation with pathological violence in adolescents, which provides evidence for the influence of both the DRD2 and DA transporter genes in pathological aggressive behavior (Chen et al., 2005). The reward deficiency syndrome (RDS), defined by Blum et al. (1996) describes a common genetic tendency, a hypodopaminergic trait (dysfunction of the D2 DA receptors), accounting for an individual predisposition to reward dependence behaviors, such as addictive, impulsive and compulsive behavioral tendencies (dependence on alcohol, psychostimulants, opiates, marijuana, nicotine, carbohydrates, PGG, sex addiction, ADHD, sensation seeking, and aggression). RDS is reported as an insensitivity to positive reinforcers (Blum et al., 2000; Comings & Blum, 2000) and/or a need to escape or avoid negative emotion (Baker et al., 2004). This is in line with Reuter et al. (2005), who demonstrated that PGG might be related to a reduction in the sensitivity of the reward system. Caldu & Dreher (2007) concluded that genetic variations in DA-related genes modify the physiological response of the dopaminergic system. This could help to explain inter-individual differences in compulsive disorders, such as PGG. In addition, the authors assumed that genetic predisposition is influenced by environmental factors, including early experience in the development of a specific behavior. Marco-Pallares et al. (2009) demonstrated within a healthy population that participants homozygous for the COMT (catechol-O-methyltransferase) ValVal allele, a dopaminergic polymorphism, showed a larger medial frontal negativity amplitude after losses and an enhanced beta power following gains in a gambling task than participants homozygous for the MetMet allele. The authors concluded, that the results plead for a lower tonic prefrontal dopaminergic activity and an enhanced striatal phasic activity in COMT Val allele carriers in comparison to Met allele carriers. This suggests that genetic differences in the dopaminergic system could be directly linked to electrophysiological responses to positive and negative reward. Further research will have to answer the question whether the reported dopaminergic

polymorphisms linked to deviations in the MFN might be an indicator of vulnerability in the development of PGG behavior.

Summarizing, genetic research provides evidence for dopaminergic, serotonergic, and norepinephrinergic components of risk in PG, which are thought to be modulated by environmental factors (Caspi et al., 2002; Caspi et al., 2003).

1.4 Addiction and cue-induced changes in the perception-action cycle

Perceived events and planned actions share a common representational domain (common-coding approach; Prinz, 1997). This means that on one hand perception affects action and on the other hand action influences perception. Addiction might be a consequence of altered perception in a way that perception of addiction-cues is facilitated by elaborated addiction-related behavior (Fehr et al., 2007b). Furthermore, perception might influence action in a way that addiction-cues trigger elaborated addiction-related action plans. In this sense perception and action could work together and, therefore, strengthen addiction severity mutually via learned perception-action cycles. This would be in line with an EEG-study of Franken (2004) who demonstrated an augmented late slow positive wave and feelings of craving during presentation of substance-related pictures in cocaine and heroin addicts. The authors linked the late slow positive wave to be an adequate index of motivational interest, which in turn might elicit motor preparation (Franken, 2003). Brewer & Potenza (2008) hypothesized that goal-directed actions transit from active learning to a more dysfunctional, habit-based response in impulse control disorders, including PGG, in a similar fashion to that observed in substance addicted individuals. The authors concluded that over-trained behavior is reflected by an activation switch from dorsolateral prefrontal cortex (DLPFC) and nucleus caudatus to putamen, representing a shift from ventral striatum to dorsal striatum (see Figure 1.3).

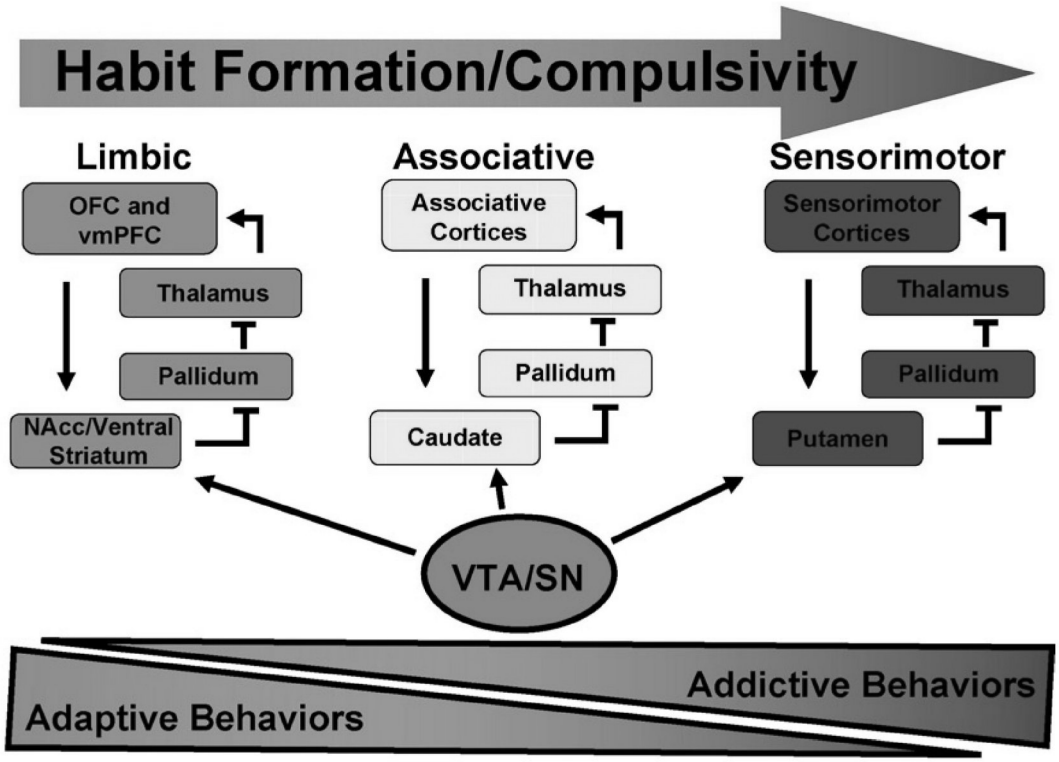

Figure 1.3 Behavior shifting from active learning to habitual response (Figure adapted from Brewer & Potenza, 2008; OFC = orbitofrontal cortex; vmPFC = ventromedial prefrontal cortex; NAcc = nucleus accumbens; VTA/SN = ventral tegmental area/substantia nigra).

Altogether, in PGG cue-induced changes in the perception-action cycle could play a crucial role in the development and long-term maintenance of gambling behavior through strengthening of cue-induced perception-action coupling.

1.5 Somatic marker hypothesis and pathological gambling

The somatic marker hypothesis (Damasio, 1994; Damasio et al., 1991) proposes that recalled stimuli from thoughts and memory, called secondary inducers, automatically create somatic states in an analogous way as primary inducers, which are innately set as pleasurable or aversive. The ventromedial prefrontal cortex (VMPFC) plays a crucial role in integrating emotion-based biasing signals upcoming from the body to control decision making in complex situations (Dunn et al., 2006), where rewarding or punishing aspects of a situation are not immediately clear (Bechara et al., 1999). Bechara (2005) defined addiction in relation to the somatic marker hypothesis as a product of an imbalance between two systems. First, the impulsive amygdala system, dealing with pain or pleasure

of immediate prospects. Second, the reflective PFC system dealing with pain or pleasure of future prospects. An important assumption of the theory is that the amygdala reacts to somatic events occurring in the environment, whereas the VMPFC activates somatic states from knowledge, cognition and memory. The somatic marker hypothesis proposes that poor decision making leads to addiction in the sense that hyperactivity in the impulsive amygdala system overrides the reflective prefrontal system.

Concerning PGG, gambling-related cues associated with positive feelings might trigger the PFC system via learned perception-action cycles (Fuster, 2006) leading in turn to an enhancement of craving or gambling behavior (Crockford et al., 2005).

1.6 Aims and scope of the present thesis

The present thesis aimed at comparing PG with OG on risk assessment and reward processing within an ecological valid gambling environment. Therefore, a quasi-realistic blackjack game is developed, which allows analyzing different stages of the game separately. First, the start of the game, when risk assessment and decision making occur and the end of the game, when reward processing takes place. Due to the predetermined sequence of the blackjack scenario it is possible to compare different levels of perceived risk during the start of the game. At the second stage of the game a differentiation between positive and negative reward processing can be made.

The goal of the first experiment (Experiment 1) is to examine the blood oxygen level dependent (BOLD) response related to risk assessment and reward processing within an ecologically valid blackjack game, comparing PG with OG.

In a second experiment (Experiment 2) the same experimental design is used to characterize temporal dynamics between PG and OG during risk assessment and winning and losing money employing EEG technique. Therefore, it is possible to combine high spatial information of the fMRI approach with a good temporal resolution of the EEG technique to gain insight into the temporal dynamics of group-specific local brain activity, underlying risk assessment and reward processing. The descriptions of both experiments start with an overview of the relevant literature to provide information about the study and its goals, including the hypotheses. This is continued by a specification of the applied methods and the derived results. In the end, the obtained results are discussed in relation to the literature.

2 Experiment 1: Risk assessment and reward processing in pathological gambling - an event-related fMRI study

2.1 Introduction - fMRI study

PGG is characterized by craving for gambling, loss of control, and continuing gambling despite associated adverse consequences. It is classified as an impulse control disorder in the DSM IV with a lifetime prevalence of 0.5 – 1 percent (Petry et al., 2005). From a clinical point of view, PGG is related to addictive behavior (Potenza, 2006) and there is emerging evidence that the underlying pathology on a neuronal level compares to cue-related behavior in drug addiction (Franklin et al., 2007). Gambling takes place in a complex social and context-specific environment which cannot easily be transferred into an experimental setting. Furthermore, the gambling situation consists of a variety of cognitive (problem solving, risk assessment, decision making) and emotional (reward processing) behaviors which may be prevalent in problem gamblers. In the present study an experimental design with a quasi-realistic blackjack game scenario was introduced to enhance ecological validity and to allow for the analysis of different episodes of the game. The particular interest of the present experiment was to separate the risk assessment and reward processing periods of the game because both have been shown to be impaired in PGG (Goudriaan et al., 2005; Reuter et al., 2005).

2.1.1 Risk assessment and reward processing in pathological gambling

Growing evidence suggests that risk assessment/decision making might be affected in PGG, especially when gamblers have to choose between risky and safe options (Bechara, 2005). So far, most experimental data has been derived from the Iowa Gambling Task (IGT), developed by Bechara et al. (1994) and introduced as a tool to measure "risk-anticipation". Patients with ventromedial frontal lobe damage (Cavedini et al., 2002), with disinhibition behavior (substance dependencies, psychopathy and ADHD; Blair, 2001), and PG (Goudriaan et al., 2005) showed impaired performance on the IGT (Bechara et al., 1997). Tanabe et al. (2007) reported a reduced activation in the right PFC during decision making in substance-dependent gamblers, as compared to substance-dependent controls on the IGT. These authors related gambling associated problems to impaired working memory, stimulus reward evaluation, or cue-reactivity. Furthermore, Brand and colleagues (2005a; 2005b) suggested dorsolateral prefrontal and orbitofrontal dysfunctions in PG.

In addition to impaired risk evaluation and risk taking, it has been shown that reward processing and the activity of the mesolimbic dopaminergic reward system (Self & Nestler, 1998; Volkow et al., 2002) may be affected in PGG. Additionally, there is evidence for a reduction in the sensitivity of the reward system. Reuter et al. (2005) compared PG to healthy controls in a simple card-guessing game and demonstrated a ventral striatal and ventromedial prefrontal hypoactivation in PG, which was positively correlated with gambling severity. D-amphetamine, a non-specific DA agonist, was shown to prime gambling motivation in problem gamblers (Zack & Poulos, 2004). This points to a deregulation of specific DA-related neuronal reward processes in problem gamblers. More recently, the same group (Zack & Poulos, 2007) demonstrated an enhancement of reward and priming effects of a gambling episode (playing slot machines) in PG as compared to non-gamblers after D2 antagonist intake.

2.1.2 Ecologically valid approach

The majority of studies investigating neuronal correlates in PGG are based on experimental settings which simplify the complex gambling environment. There are only a few studies which have introduced a more ecologically valid experimental gambling design to examine neuronal or neuroendocrinological responses while playing. Two experiments recorded event-related potentials (ERPs) (Hewig et al., 2007; Yang et al., 2007) during a blackjack game and are further specified in chapter 3.1.1. Hewig et al. (2009) showed in a fMRI study that suboptimal decisions (too risky and too cautious) in a modified blackjack game were related to increased activity in the dorsal ACC. The authors concluded that these results were in line with the reinforcement learning principle (Holroyd & Coles, 2002) since increased dorsal ACC activity was associated with the avoidance of negatively evaluated decisions. Meyer et al. (2004) compared the neuroendocrine responses of problem gamblers and of healthy controls in two different situations: A real blackjack casino situation, where gamblers invested their own money and an experimental control condition, where participants were playing for points in a laboratory environment. The results showed higher levels of NE and DA in problem gamblers in a “real money” casino environment, which became insignificant in the control condition. Thus, it was decided to design the present experimental blackjack game scenario to be as realistic as possible, while considering necessary experimental efforts for methodologically correct parameterization.

2.1.3 Hypotheses and goals of the study

The present study aimed at:

1) analyzing both parts of the game, the periods of risk assessment and reward processing.

2) using an ecologically valid quasi-realistic blackjack scenario with comparatively high wages.

3) a comparison of PG and OG by use of fMRI.

Based on the above-mentioned studies, we expected that especially in problem gamblers both risk assessment and reward processing might be modulated by the gambling-related nature of the applied task: 1) For the period of risk assessment, we expected a signal increase in inferior frontal/orbitofrontal and thalamic brain regions, especially in problem gamblers during high risk situations; 2) During reward processing, we hypothesized a signal increase in the nucleus accumbens in both groups after winning money. The quasi-realistic task, including gambling for real money, was supposed to counteract or override general observed hypoactivation in pathological gamblers' brain regions associated with risk assessment and reward processing as reported for experimental setups with a lower gambling-authenticity.

2.2 Methods - fMRI study

2.2.1 Study participants

The study group consisted of 12 healthy male OG (mean age 33.4 ± 8.0 years; range 25 - 49 years) and 12 male PG (mean age 39.5 ± 9.3 years; range 29 - 57 years). All participants were right handed according to a modified version of the Edinburgh Handedness Questionnaire (Oldfield, 1971). Both groups did not differ with respect to age [($F_{[1,22]}$=2.97, p=0,1] and smoking behavior (z=-1.7, p=0.1). It was decided to investigate only male participants, as the prevalence of PGG in men is reported to be two times higher than in women (Grant & Potenza, 2004). Participants were recruited through advertisements and were familiarized with the gambling environment in the laboratory. Frequency of gambling was significantly higher in PG compared to OG (PG: mean: > 3 times / week; OG: mean: ≤ 3 times / month; z=-2.7, p < .01). PG and OG did not differ with respect to the frequency of blackjack gambling (z=-0.6, p=0.6). Prior to enrollment in the study, all participants underwent a structured psychiatric interview. OG did not report a history of psychiatric or neurological illness or regular drug use and were not under current medication. In the PG group, five participants were presented with a diagnosis of problem gambling (3 or 4 criteria; Toce-Gerstein et al., 2003) and seven participants had a diagnosis of PGG (≥ 5 criteria) according to DSM IV (see appendix A 6). Furthermore, all individuals were assessed with the German gambling questionnaire "Kurzfragebogen zum Glücksspielverhalten" (KFG; Petry, 1996; derived from 20 items as developed by "Gamblers Anonymous"; see also appendix A 7). Instrumental (Cronbach's alpha = .79) and retest (r = .80) reliability of the scale are reported to highly fulfill the psychometric properties of a screening instrument (Petry, 1996). This questionnaire contains 20 items (4-point Likert-scale: 0 to 3 points) addressing lifetime gambling behavior. The threshold for PGG is set at 16 points. All PG scored between 18 and 45 points (mean 28.2 ± 7.9), whereas OG scored between 0 and 12 points (mean 5.3 ± 3.7). In addition, all participants were evaluated with a German version of the South Oaks Gambling Screen (SOGS; Lesieur & Blume, 1987b; see appendix A 8). Participants who scored ≥ 5 points were classified as "probable pathological gamblers". All PG scored ≥ 6 on the SOGS (mean 10.7 ± 3.8) and OG obtained ≤ 2 (mean 0.7 ± 0.7).

2.2.2 Data protection, data security and legal framework

The study protocol was designed according to the Code of Ethics of the World Medical Association (Rickham, 1964) and was approved by the local ethics committee. All participants were informed about their right to quit the experiment at any time without giving reasons (see appendix A 1), data collection, data protection and data security, and gave written informed consent to participate prior to the fMRI measurement (see appendix A 3). In addition, participants were also informed about the fMRI method and the risks of fMRI measurement (see appendix A 1 and it was proved whether they fulfilled the exclusion criteria for fMRI (see appendix A 2). Furthermore, participants were naïve to the experimental design and the working hypotheses of the current study.

2.2.3 Experimental design

The experimental blackjack task consisted of 206 trials (50 low-risk, 50 high-risk, 50 fill, and 56 validity trials). The low-risk trials reflect situations in which the player started with 12 or 13 points against the dealer's 7, 8, 9, or 10 points. High-risk trials consisted of the player with 15 or 16 points and the dealer with 7, 8, 9, or 10 points. Participants were informed that they played against the computer. The probability of losing while drawing a card [p(lose|hit)] over all low-risk trials was 0.34 and 0.56 over all high-risk trials. Fill-trials were composed of cards with pictures and numbers with no relation to the blackjack game, which served as low-level baseline condition in further analyses not reported here. Furthermore, 56 validity-trials were included, consisting of aces (1 or 11 points) and starting-situations with 14, 17, 18, 19, 20 or 21 points for the player. These validity-trials should guarantee a quasi-realistic blackjack scenario. Both fill- and validity trials were modeled separately and excluded from further analyses. The bet was fixed at € 5 in low-risk and high-risk trials and at € 1 in validity-trials.

All trial elements were presented against a black background. A trial started with a jeton representing a fixed bet (€ 1 or € 5; frame 1, see Figure 2.1a) for 500 milliseconds (ms), followed by a white fixation point for 1500 ms (frame 2). Thereafter, three cards were presented for a maximum of 6000 ms; on the upper part of the screen one card for the dealer and on the lower two cards for the player (frame 3). Within this period the player had to decide whether he wanted to hit ("take another card"; right mouse: left button click; index finger) or to stand ("no further card required"; right mouse: right button click; middle finger, frame 4). Thereafter, the dealer took cards according to the official blackjack rules (the dealer must hit until his total was 17 or higher). Dependent on the

player's response (hit or stand), the dealer started to take another card 300 ms (after the player decided to stand and 2000 ms after the player hit. The end of the round was presented for 3000 ms (frame 5), followed by a 2000 ms information screen displaying the running total of the player (frame 6) and a 2000 ms inter-trial fixation point (frame 7).

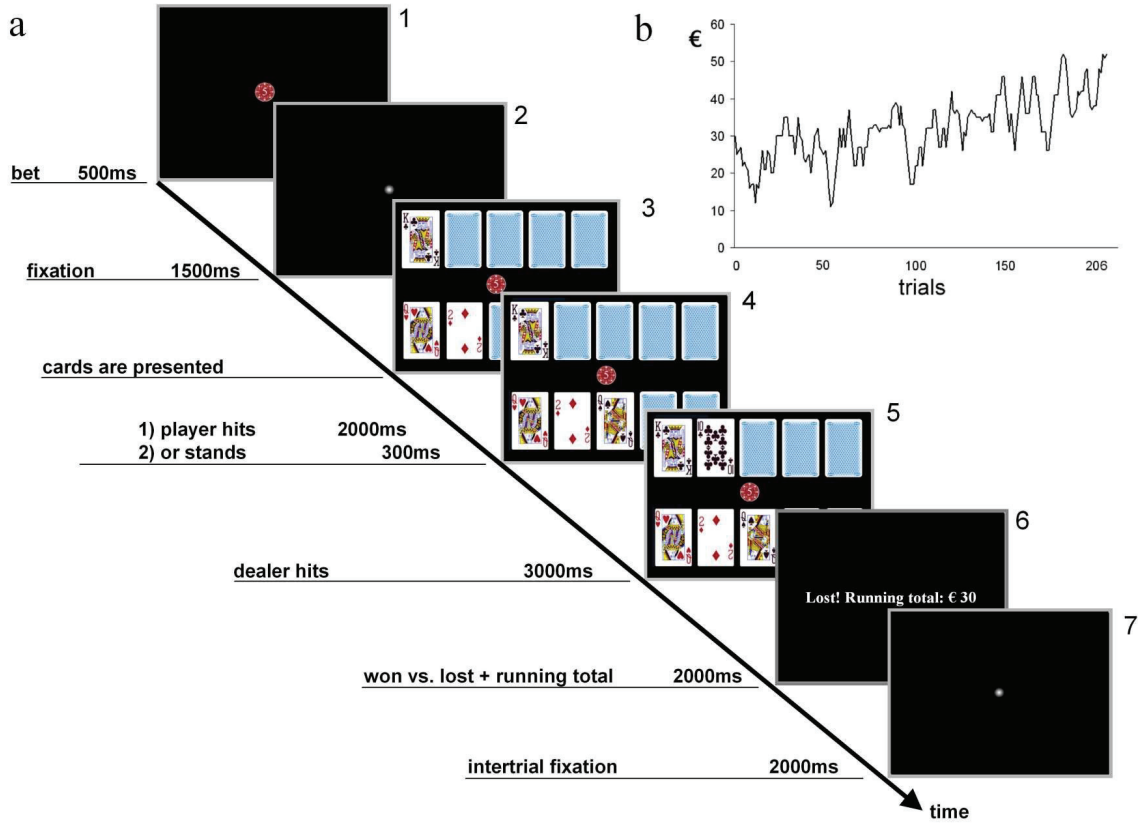

Figure 2.1 (a) Trial description of and task elements in a quasi-realistic blackjack scenario, (b) predetermined course of the game.

At the beginning of the game, each player started with a balance of € 30. All study participants were informed that they might lose some of this starting balance and that they would receive the entire balance in cash at the end of the experiment. Wins and losses followed a predetermined course independent from the player's decisions (see Figure 2.1b). Trials were presented in a pseudo-randomized non-stationary probabilistic sequence (Friston, 2000). Participants lost 50 percent of the high-risk trials and 50 percent of the low-risk trials, and always finished the game with a total amount of € 52. In contrast to official blackjack rules the player was allowed to hit or to stand only one time per round. Furthermore, splitting or doubling was not permitted.

2.2.4 fMRI data acquisition

While participants performed the tasks, functional MRI data were collected on a 3 Tesla Siemens Allegra scanner (Siemens, Erlangen, Germany) using a gradient echoplanar imaging (EPI) sequence covering 44 axial (anterior commissure–posterior commissure), interleaved slices (3 mm thick) encompassing the entire cerebrum and cerebellum (TR/TE=2500/30 ms; FOV 192 mm). About 1000 volumes were obtained during each run. A T1-weighted structural 3D-image of the brain was obtained using the MPRAGE-sequence: 160 contiguous slices, TR = 2.3 s, TE = 4.38 ms, TI = 900 ms, FA=8°, FOV 296 x 296 mm, in-plane resolution 1 x 1 mm, slice thickness 1 mm.

2.2.5 fMRI data analysis

Image analysis was performed using SPM2 (http://www.fil.ion.ucl.ac.uk/spm/). For each session and participant, images were realigned to the tenth image in the time series to correct for head motion. These realigned images were spatially normalized into a standard stereotactic space (Montreal Neurological Institute template) using a 12 parameter affine model. These spatially normalized images were smoothed to minimize noise and residual differences in gyral anatomy with a Gaussian filter set at 8 mm. Prior to statistical analysis a high pass filter (500 s) was applied to remove global effects. Pre-processed data sets were analyzed using a second-level random effects model that accounts for both scan-to-scan and participant-to-participant variability (Holmes, 1998). Several trial elements and periods were modeled exclusively by the standard hemodynamic response function, and included as separate predictors (high-risk, low-risk, fill, validity, response, win, lose, equal, running total) in the design matrix. To compare PG and OG, second-level analyses were performed by calculating t-statistics including first level contrast images for predetermined condition effects at each voxel for each participant and session for the following contrasts: high-risk vs. low-risk, low-risk vs. high-risk, win vs. lose, and lose vs. win. In a first analysis, voxels showing a main effect of high-risk vs. low-risk, and low-risk vs. high-risk ($p<.001$ uncorrected, $k>5$) were determined. An interaction analysis was calculated to test for voxels, showing larger contrasts in PG than in OG and vice versa. To restrict the search volume to active regions showing a significant main effect of high-risk vs. low-risk or low-risk vs. high-risk respectively, the interaction analyses were masked inclusively by the corresponding contrast of the first group entered in the analysis ($p<.001$ uncorrected; $k>5$). Thus, for an interaction analysis PG vs. OG, the main effect of PG was entered as an

inclusive mask. The same analysis was calculated as described above for the win vs. lose and lose vs. win conditions (FWE, $p<.05$; $k>20$), as well as interaction analyses to compare groups (PG vs. OG; OG vs. PG; $p<.001$, $k>5$). Furthermore, conjunction analysis (conjunction null; Nichols et al., 2005) was calculated including win vs. lose conditions for PG and OG ($p<.05$, FWE-corrected, $k>20$). Estimates of percentage signal change in the high-risk, low-risk, win, and lose conditions were extracted from brain regions for each participant using MarsBaR (Brett et al., 2002).

For the identification of activated anatomical structures, MNI (Montreal Neurological Institute) template-based coordinates were transformed into Talairach coordinates (Talairach & Tournoux, 1988) using a matlab tool (mni2tal.m, http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach) and determined the anatomical regions using the Talairach Daemon Client software (http://ric.uthscsa.edu/projects/talairachdaemon.html).

2.3 Results - fMRI study

2.3.1 Behavioral data

Response times (RT) and decision behavior (hit vs. stand) in PG and OG did not differ significantly. A repeated measures ANOVA for RTs with the factors group (PG vs. OG) x risk (high-risk vs. low-risk) showed no significant main effect of group ($F_{[1,22]}$=0.9; p=0.3; PG: low-risk 1560±417 ms, high-risk: 1992±576 ms; OG: low-risk 1361±481 ms, high-risk: 1772±684 ms), and group x risk interaction ($F_{[1,22]}$=0.02; p=0.9). Both groups showed significantly longer RTs in high-risk compared to low-risk conditions (main effect of the factor risk; 1882±629 ms vs. 1461±452 ms; $F_{[1,22]=}$42.9, p<.001).

In addition, PG and OG did not differ in decision behavior. A repeated measures ANOVA for decision behavior with the factors group (PG vs. OG) x decision behavior (percent high-risk hit vs. percent low-risk hit) revealed no significant main effect of group ($F_{[1,22]}$=0.43; p=0.5), and group x decision behavior interaction ($F_{[1,22]}$=0.02; p=0.9). Both groups showed significantly lower percentage of high-risk compared to low-risk hit trials (main effect of the factor decision behavior; $F_{[1,22]=}$52.8, p<0.001; PG low-risk: 93.8±11.1 percent, high-risk: 61.2±25.7 percent, OG low-risk: 97.2±5.8 percent, high-risk: 65.7±22.7 percent).

2.3.2 Functional imaging data

The analysis of functional MRI data was restricted to low-risk and high-risk trials. Furthermore, it was focused on two different time periods in the trials: 1) risk assessment and preparatory decision making, and 2) win or lose situations. The first time period covered the presentation of the cards until the player's decision (see Figure 2.1 frame 3 to 4), the second period covered the time between the dealer's hit and the presentation of the information of winning or losing and the running total (see Figure 2.1 frame 5 to 6). If the player's decision to hit resulted in a higher total than 21 (i.e., he lost the game) the second period covering win or lose perception was restricted to frame 4 to 5.

Neural correlates of risk assessment, as revealed by contrasting high-risk vs. low-risk conditions, resulted in significant activation patterns in PG (p<.001, uncorrected) including bilateral frontal, temporal, right parietal, bilateral parahippocampal, and right thalamic regions (see Table 2.1 A and appendix A 10).

Table 2.1 Brain regions activated during risk assessment - Talairach coordinates, anatomical regions and t-scores of high-risk > low-risk task contrasts for PG (A) and OG (D), and low-risk > high-risk contrasts for OG (C) and PG (B) (all p<.001, uncorrected, k=5).

		A					B	C					D
		high-risk$_{PG}$ > low-risk$_{PG}$					low-risk$_{PG}$ > high-risk$_{PG}$	low-risk$_{OG}$ > high-risk$_{OG}$					high-risk$_{OG}$ > low-risk$_{OG}$
Regions	**H**	**t**	**cl-size**	**X**	**Y**	**Z**		**t**	**cl-size**	**X**	**Y**	**Z**	
Superior Frontal Gyrus	L	4.22	6	-10	30	57		3.98	23	-2	7	57	
Inferior Frontal Gyrus	R	4.74	61	48	44	-6							
Precentral Gyrus	R							3.84	7	20	-16	63	
Postcentral Gyrus	R							3.88	9	42	-18	25	
Middle Temporal Gyrus	R	4.46	82	67	-25	-2							
Superior Temporal Gyrus	L	4.28	11	-44	24	-18							
	R							4.77	186	67	-21	8	
	R							4.49	186	53	-13	6	
	R							4.00	186	59	-31	9	
	R							3.68	8	44	-29	9	
Inferior Parietal Lobe	R	3.77	6	44	-50	54							
Supramarginal Gyrus	R	4.66	122	55	-55	32							
Inferior Parietal Lobe	R	3.83	122	48	-54	45							
Parahippocampal Gyrus	L	4.84	15	-18	-13	-28							
	R							3.69	6	28	-45	-3	
Thalamus	L							4.12	77	-6	-23	10	
	R	4.09	21	8	-33	2		3.75	77	6	-23	10	
Insula	R							3.77	8	42	-28	18	

Table 2.2 Interaction analyses of brain regions activated during risk assessment - Talairach coordinates, anatomical regions and t-scores of the between group comparisons in the high-risk > low-risk task contrasts for PG vs. OG (A) and in the low-risk > high-risk task contrasts for OG vs. PG (B) (all p<.001, uncorrected, k=5).

		A					B				
		(high-risk$_{PG}$ > low-risk$_{PG}$) > (high-risk$_{OG}$ > low-risk$_{OG}$)					(low-risk$_{OG}$ > high-risk$_{OG}$) > (low-risk$_{PG}$ > high-risk$_{PG}$)				
Regions	**H**	**t**	**cl-size**	**X**	**Y**	**Z**	**t**	**cl-size**	**X**	**Y**	**Z**
Inferior Frontal Gyrus	R	3.92	18	46	42	-5					
Superior Temporal Gyrus	R	4.28	50	67	-25	1	5.25	80	67	-21	8
	R						4.34	50	53	-13	6
	R						4.75	80	59	-31	7
	R						3.97	8	44	-27	7
Thalamus	L						3.75	11	-2	-25	9
	R	3.93	8	10	-33	3					

The reverse contrast, revealed activation patterns in OG (p<.001 uncorrected; see Table 2.1 and appendix A 11) in bilateral frontal, right superior temporal, bilateral thalamic, insular, and parahippocampal regions.

This dissociation was confirmed by an interaction analysis showing larger contrasts in OG compared to PG for low-risk vs. high-risk conditions [right superior temporal gyrus (STG) and left thalamus; see Table 2.2 B and appendix A 12] and a significant percent signal increase in PG compared to OG in right STG, right inferior frontal gyrus (IFG), and right thalamus (see Table 2.2 A and Figure 2.2).

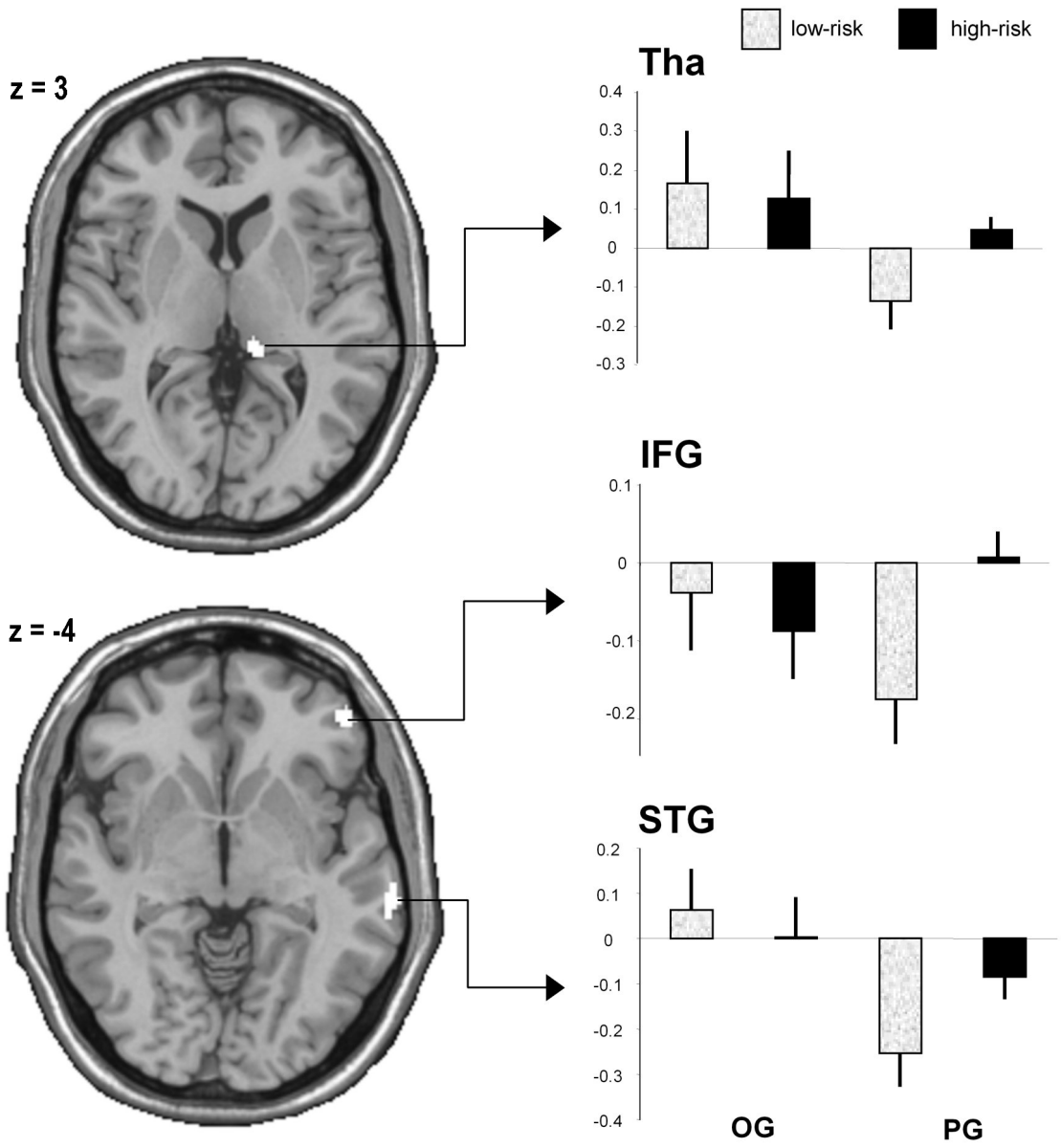

Figure 2.2 Activation pattern and percent signal change (± 1 SEM) derived from the high-risk > low-risk contrast in PG vs. OG (p<.001 uncorrected) in the pulvinar nucleus of the Thalamus (Tha), inferior frontal gyrus (IFG), and superior temporal gyrus (STG). MNI to Talairach transformed coordinates are given in Table 1.

Table 2.3 Brain regions activated during reward processing - Talairach coordinates, anatomical regions and t-scores of win > lose task contrasts in PG (A), OG (B) (p<.05, FWE corrected; k=20).

		A					B				
		$win_{PG} > lose_{PG}$					$win_{OG} > lose_{OG}$				
Regions	**H**	**t**	**cl-size**	**X**	**Y**	**Z**	**t**	**cl-size**	**X**	**Y**	**Z**
Middle Frontal Gyrus	L	11.01	2823	-30	-7	59					
	R	9.94	283	34	3	55					
	R	7.78	283	30	-1	61					
	R	6.75	283	42	0	48					
Precentral Gyrus	L	7.25	32	-53	2	33					
	R	7.11	23	46	-16	36	7.28	20	44	-14	30
Subcallosal Gyrus	L						6.41	52	-14	5	-14
	R	9.50	308	18	7	-14	8.91	209	16	5	-14
Superior Frontal Gyrus	L						7.12	26	-28	-1	63
	R	9.33	69	24	15	58					
Superior Temporal Gyrus	L	6.84	28	-42	-25	5					
	R	7.43	32	48	-19	3					
Postcentral Gyrus	R	9.79	479	57	-23	44					
Inferior Parietal Lobe	R	7.97	479	44	-38	55					
Postcentral Gyrus	R	6.99	479	46	-29	40					
Precuneus	L	11.87	2823	-30	-48	52	7.24	43	-18	-59	56
	R	6.72	45	26	-68	48					
Lingual Gyrus	L	10.24	238	-16	-58	5	8.88	88	-22	-95	-5
	L	7.50	203	-10	-82	-3	7.64	562	-10	-76	-5
	R	6.85	33	2	-74	-8					
Cuneus	L	8.31	106	-20	-99	0	7.58	562	-8	-79	8
	L	7.80	203	-8	-79	8	6.33	146	-4	-87	14
	L						7.13	32	-12	-60	9
	R	7.96	56	16	-96	23	7.52	146	12	-89	6
	R						7.32	146	12	-94	25
	R						6.48	29	16	-71	16
	R						7.34	22	6	-91	12
Fusiform Gyrus	R	7.26	34	26	-53	-7					
Lentiform Nucleus, Putamen	L	6.81	52	-30	-12	2					
	R	6.97	55	26	6	11					
	R	6.59	22	32	-16	1					
	R	7.18	55	26	10	1					
Claustrum	L	6.70	28	-36	-25	0					
Posterior Cingulate	R	6.95	26	16	-65	16	6.83	29	22	-62	7
	R						6.59	29	18	-63	14
Nucleus Accumbens	L	9.63	265	-8	9	-7	7.61	52	-8	9	-7
	R	9.56	308	10	7	-9	8.58	209	10	9	-9
Cingulate Gyrus	L	10.74	432	-2	-28	33					
	R						7.80	74	2	-24	29
Thalamus	L	8.32	436	-8	-17	1	7.20	89	-10	-15	10
	L	7.33	436	-12	-21	14	6.93	89	-16	-15	15
	L	7.24	436	-20	-25	1					
	R	8.50	241	10	-21	1	7.08	30	18	-27	11
	R	8.03	241	16	-17	6					
Cerebellum	L						7.75	562	-4	-74	-10
	R	7.75	93	2	-77	-23					
	R	7.29	93	10	-77	-18	7.32	51	24	-63	-12

Table 2.4 Brain regions activated during reward processing - Talairach coordinates, anatomical regions and t-scores of (A) a conjunction (null) analysis including win > lose contrasts of PG and OG (p<.05, FWE-corrected; k=20), and (B) between group comparison (PG vs. OG) in the win > lose contrast (p<.001, uncorrected, k=20).

		A					B				
		Conjunction (null) ($win_{PG} > lose_{PG}$) & ($win_{OG} > lose_{OG}$)					($win_{PG} > lose_{PG}$) > ($win_{OG} > lose_{OG}$)				
Regions	**H**	**t**	**cl-size**	**X**	**Y**	**Z**	**t**	**cl-size**	**X**	**Y**	**Z**
Subcallosal Gyrus	L	6.41	52	-14	5	-14					
	R	8.91	187	16	5	-14					
Superior Frontal Gyrus	L	7.12	23	-28	-1	63					
	R						4.67	23	24	15	56
Inferior Parietal Lobe	L						4.68	86	-32	-55	44
Superior Parietal Lobe	L						4.03	86	-28	-50	55
Precuneus	L	7.24	42	-18	-59	56					
Lingual Gyrus	L	7.48	66	-22	-95	-5					
	L	7.13	87	-10	-80	-3					
Cuneus	L	7.58	87	-8	-79	8					
	L	7.94	66	-18	-99	0					
	L	7.13	31	-12	-60	9					
Nucleus Accumbens	L	7.61	52	-8	9	-7					
	R	8.58	187	10	9	-9					
Cingulate Gyrus	R	7.80	72	2	-24	29					
Thalamus	L	7.20	65	-10	-15	10					
	L	6.73	65	-16	-17	16					
Cerebellum	L	6.59	76	-4	-73	-20					
	R	7.51	76	2	-77	-23					
	R	7.29	76	10	-77	-18					
	R	6.85	31	2	-74	-8					

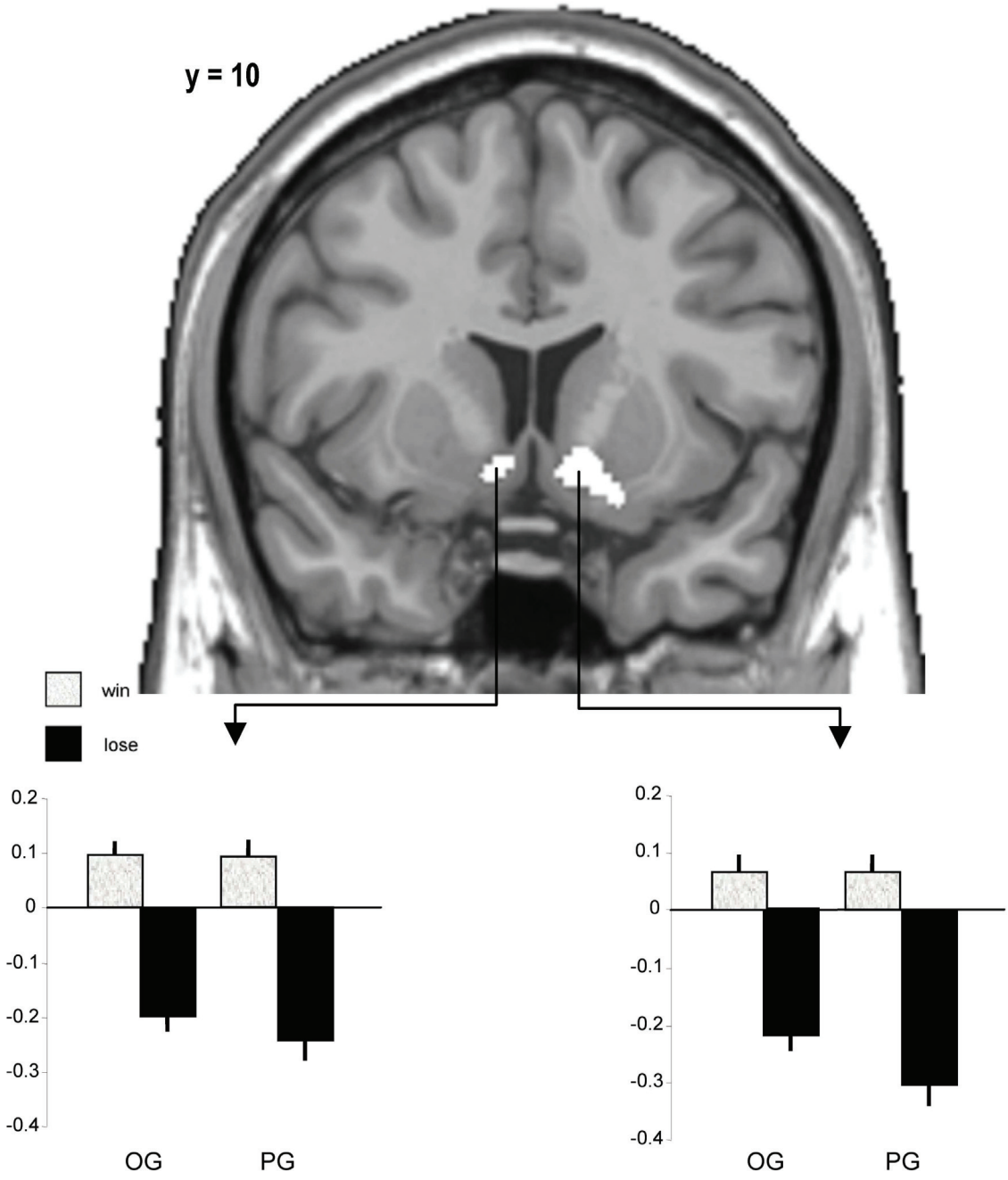

Figure 2.3 Activation pattern and percent signal change (± 1 SEM) derived from the win > lose contrast in the conjunction (null) analysis for OG and PG (p<.05 FWE-corrected) in the nucleus accumbens. MNI-to-Talairach-transformed coordinates are given in Table 2.4 A.

Contrasting win vs. lose conditions (p<.05; FWE-corrected) produced widespread bilateral parietal, occipital, frontal, and subcortical activation patterns in both PG and OG (see Table 2.3 A and B; see also appendix A 13 and A 14).

A conjunction analysis (p<.05, FWE-corrected; see Nichols & Hayasaka, 2003) demonstrated that both groups showed common activation patterns in brain regions related to reward processing [Ncl. accumbens, bilateral frontal regions, left parietal regions (precuneus), left occipital regions, bilateral cerebellum, left thalamus, and right posterior cingulate gyrus; see Figure 2.3 and Table 2.4a].

Comparing activation patterns in win vs. lose situations between groups (win > lose) PG vs. OG; threshold p<.001, uncorrected, see Figure 2.4 and Table 2.4 B) resulted in right superior frontal, left inferior parietal, and left superior parietal signal increases; whereas the opposite contrast (OG > PG) for the win vs. lose condition became not significant. Furthermore, lose situations compared to win situations did not show suprathreshold activations.

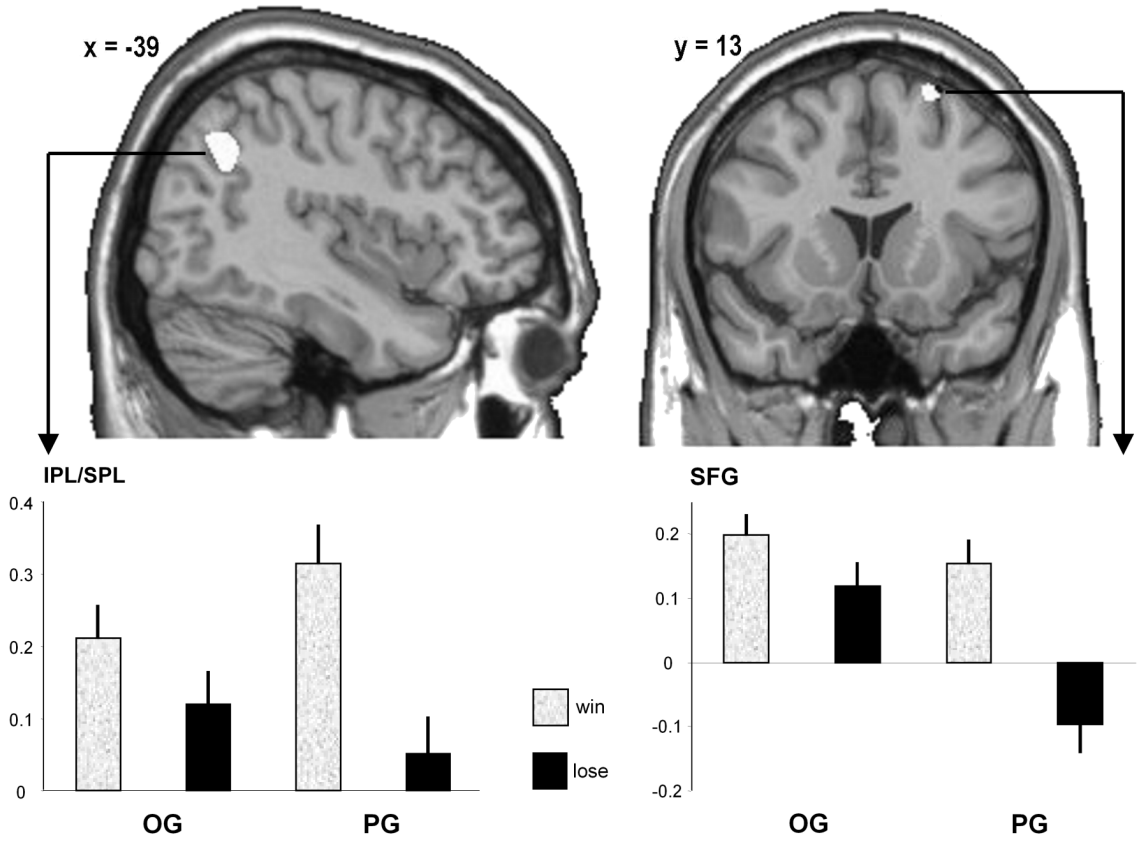

Figure 2.4 Activation patterns and percent signal change (± 1 SEM) resulting from the win > lose contrast in PG vs. OG (p<.001 uncorrected) in the inferior parietal lobe/superior parietal lobe (IPL/SPL) and superior frontal gyrus (SFG). MNI-to-Talairach-transformed coordinates are given in Table 2.4 B.

2.4 Discussion - fMRI study

Using fMRI, neuronal correlates in PG and OG during a quasi-realistic blackjack scenario were investigated with respect to risk assessment and as to reward processing. The present data suggest that risk assessment was associated with comparable arousal-related neuronal networks in PG and OG. During high-risk situations, fronto-thalamic brain activity was enhanced in PG, whereas OG showed a significant signal increase in low-risk conditions. Winning contrasted with losing money activated brain regions associated with reward processing in both PG and OG, whereas an interaction analysis between groups resulted in significantly larger contrasts in fronto-parietal regions in PG as compared to OG.

2.4.1 Risk assessment

Behavioral data derived from the risk assessment period of the game did not show differences in the percentage of hit trials between groups, but significantly slower RT for high-risk situations in both groups. These data indicate that PG and OG did not differ on a behavioral level and that PG did not run a higher risk during the present blackjack game. The surplus in RT in high-risk situations might be associated with a higher amount of response conflict (Yang et al., 2007). Although behavioral data were comparable in both experimental groups, imaging data analysis during risk assessment showed group-related differences.

A region of interest analysis based on percent signal change values indicated a dissociation between OG and PG in STG, right inferior frontal gyrus (IFG), and right medio-pulvinar brain regions. OG presented increased activity during low-risk situations, whereas PG showed a signal increase in high-risk trials.

The thalamus had been shown to be involved in addictive behavior as reported by a variety of studies (Breiter et al., 1997; Due et al., 2002; Franklin et al., 2007; George et al., 2001; Potenza et al., 2003a; Potenza et al., 2003b; Wang et al., 2007). The medial pulvinar nucleus of the thalamus is reciprocally interconnected with the cingulate gyrus and other limbic structures (Morgane et al., 2005) and is considered to play a crucial role in learning and memory (Mitchell et al., 2008), emotional experience and expression (Nummenmaa et al., 2008), drive (Sewards & Sewards, 2003), and motivation (Schmahmann, 2003). In addition, Leh et al. (2008) showed that human pulvinar was interconnected with subcortical structures (superior colliculus, thalamus, and caudate nucleus) as well as with cortical regions [primary and secondary visual areas, inferotemporal brain regions,

posterior parietal association areas (area 7), frontal eye field, and prefrontal areas]. These data demonstrate the important role of the pulvinar in human visual information processing and visuospatial attention. However, the direction of the neuronal response is under discussion. Tomasi et al. (2007) reported a hypo-activation of the medio-dorsal thalamus and the lateral geniculate body of the thalamus in cocaine abusers during a visuo-spatial attention task, whereas George et al. (2001) showed alcohol cue-induced dorsolateral-prefrontal and anterior thalamus signal enhancement in alcoholics if compared to healthy controls. Wang et al. (2007) demonstrated that right thalamus, orbitofrontal, and DLPFC activation was related to abstinence-induced craving in smokers. These findings might reflect a dissociation within thalamic activity with respect to an addiction-related environment of the task. In common decision making paradigms (not referring to addiction-related stimulus material) there is evidence for a thalamic down-regulation in PG analogous to observed effects in cocaine users (Goldstein et al., 2007; Tomasi et al., 2007), whereas addiction-related stimulus material seem to enhance thalamic activity in PG, reflecting cue-induced craving engagement.

Furthermore, the IFG was found to be differentially activated in PG and OG in the high-risk vs. low-risk contrast. Potenza et al. (Potenza et al., 2003b) related decreased activation in the right OFC, basal ganglia, and thalamus in PG compared to controls, while viewing videotaped scenarios with gambling content, to impulse regulation. Crockford et al. (2005), however, showed increased right dorsolateral prefrontal and right parahippocampal activity in PG when compared to controls during viewing gambling-related video material. The conflicting data were discussed with respect to differences in stimulus material and cue-induced craving (Wilson et al., 2004). These data might indicate that both IFG as well as the medial-pulvinar activation in high-risk situations might reflect a cue-induced signal increase in PGG. High-risk situations, characterized by physiological arousal, euphoria, distraction, and perceived control (Legg England & Gotestam, 1991), might serve as an addiction-cue in PG, while the low-risk situation signalizes a “safe” hit in OG.

The higher right STG activation in high-risk vs. low-risk task conditions in PG might be related to feature-based serial exploratory search (Ellison et al., 2004) or intuitive judgments (Ilg et al., 2007). In the present task environment, the right STG might have been important in updating the card constellation, especially in PG, for preparing a hit or a stand, particularly in high-risk cases.

To conclude, neuronal correlates of PGG in the present quasi-realistic blackjack scenario might be characterized by an "expectancy-shift" from looking for secure low-risk conditions in OG to seeking for thrilling high-risk situations in PG.

2.4.2 Win or lose situations and reward processing

The NAc showed a signal increase in win situations and a signal decrease in lose situations in both PG and OG. The dopaminergic reward system was shown to be sensitive for reward processing in gambling (Reuter et al., 2005). The present findings revealing a consistent ventral striatal signal increase across groups corroborate the crucial role of the NAc in human reward processing (Knutson et al., 2001). In contrast to Reuter et al. (2005), a differential activation of the accumbens in PG and controls was not found. This finding might be related to differences in the experimental task. In the study of Reuter et al. (2005), participants of a simple card guessing game realized the moment of winning/losing the game immediately, whereas in the present quasi-realistic blackjack scenario, participants had first to calculate the sum of the card-values before perceiving the win or loss information. Therefore, the relative high stimulus-complexity in the present experiment might have modulated reward processing (Fehr et al., 2007a).

Comparing PG with OG in the win vs. lose condition resulted in left inferior parietal, left superior parietal, and right premotor activations. The inferior parietal sulcus adjoining to superior parietal and inferior parietal cortex has been reported to be activated during number tasks (Dehaene et al., 2003) and is expected to play a crucial role in the amodal representation of quantity (Dehaene et al., 2004). Smolka et al. (2006) described left inferior parietal and right premotor cortex activation in a smoking cue paradigm and demonstrated that brain activity in these regions correlated positively with the degree of nicotine dependence. Therefore, left parietal and right premotor activation, frequently associated with visuospatial attention (Kirino et al., 2000; McCarthy et al., 1997), motor preparation (Toni et al., 2002), and imagery (Rizzolatti & Craighero, 2004) might reflect neuronal correlates to the preparation of further gambling activity. Corroborating this line of argumentation, Fehr and colleagues (2007a; 2006) discussed early and late fronto-parietal ERP-differences between smokers and non-smokers during different nicotine-cue interference tasks as being related to addiction memory-related cue driven activation of neurally established perception-action cycle networks.

2.4.3 Conclusion

The present data suggest that PGG within a quasi-realistic and ecologically valid experimental setting was reflected in differential brain activation patterns during risk assessment and during reward processing. High-risk situations enhanced arousal-related brain networks in PG, whereas low-risk situations activated similar brain areas in OG. High-risk situations as well as winning money might serve as central addiction-cues for PG, which in turn activate addictive gambling behavior. In contrast to recent findings, the present data did not point to an alteration of reward-related activity in the accumbens in PG.

2.4.4 Critical reflections and limitations of the present study

The fMRI study showed differences between PG and OG in the cognitive processes of risk assessment and reward processing.

In comparison to previous studies using simple designs such as card guessing (Reuter et al., 2005) the present experimental design focused on ecological validity. The used quasi-realistic blackjack environment might have influenced risk assessment and reward processing in PG at a different level than in OG. Therefore, the observed results might be a combined effect of enhanced risk and gambling cue processing in PG. Although it was controlled for the frequency of playing blackjack it might be the case that PG were more familiar with risky decision making and winning and losing in general. Especially during winning and losing of money the quasi-realistic blackjack environment might have compensated generally weakened reward processing in the accumbens in PG.

During risk assessment the enhancement of arousal-related brain networks with the thalamus as core region seem to play a crucial role in both groups. Exciting high-risk situations might be attractive for PG whereas OG seek for save low-risk situations. The underlying motivation of PG might be an enhancement of thrill, whereas OG prefer a secure basis for preparing a risk-dependent decision. Both groups may share the volition of maximal performance in these group-specific favored situations, driven by similar arousal-related brain activity.

There are several limitations of the present study. First, the OG group did not represent "normal control participants" as described in other studies. This resulted from the intention to test individuals being equal familiar with blackjack as PG without demonstrating pathological gambling behavior. Consequently, PG and OG were rather similar related to gambling experience than groups in studies comparing PG with control participants on gambling-unrelated tasks. Second, only 7 out of 12 PG fulfilled the DSM IV criteria for PGG, whereas 5 had a diagnosis of problem gambling. Hence, it could be the case that the PG group of this experiment suffered from a milder form of PGG, although all participants in the PG group fulfilled the SOGS and KFG criteria for PGG.

3 Experiment 2: An EEG study on risk assessment and reward processing in pathological gambling

3.1 Introduction - EEG study

This study aimed to explore risk assessment and reward processing in PGG with a better time resolution than in experiment 1 and, therefore, was accomplished using EEG. This method allows to record synchronous activity of postsynaptic neuronal potentials with electrodes on the head-surface of the participant. After recording a continuous signal over the duration of the whole experiment, parts of the data (epochs) can be locked relative to an event of interest and averaged to an ERP, while the signal related to this event cumulates and noise cancels out. The next paragraphs give a short overview of important ERP components possibly modulated in PGG. At the end of the introduction the main hypothesis and goals of the study are described.

3.1.1 ERP components associated with risk assessment and reward processing in pathological gambling

There are only two studies measuring ERPs during a blackjack game - both in healthy participants. Hewig et al. (2007) demonstrated an increased error-related negativity (ERN) connected to negative evaluation of ongoing decisions, with the amplitude of the ERN being correlated with both risk taking and decision making behavior. The ERN is assumed to be generated in the ACC with a strong connectivity to the limbic system, the motor system, and to prefrontal regions (Ridderinkhof et al., 2004). Because phases of risk assessment and reward processing required a stimulus-locked analysis of the ERP data (see also chapter 3.2.5) the ERN as a response-locked component is not further described in this introduction. In addition, Yang et al. (2007) measured ERPs during high-conflict (probability of losing around 50 percent) and low-conflict conditions (probability of losing around 20 percent) in a modified blackjack game. The authors reported the N2 component to be associated with perceptual conflict and a later negative deflection between 500 and 600 ms to be related to response conflict with a higher amplitude in high-conflict as compared to low-conflict situations (see also chapter 3.1.1.4).

3.1.1.1 N1 component and attentional modulation

The N1 component refers to the first negative deflection in the ERP curve around 100 ms after stimulus presentation with a peak-variety of 100-150 ms post stimulus (Naatanen & Picton, 1987). Hillyard (1993) reported that the N1 component was sensitive to the attentional processing of stimuli. The author reported an enlargement of the P1, N1, and N2 components in a spatial attention task, when participants attended a visual stimulus. Further evidence of early attention modulation of the N1 comes from Rif et al. (1991), who reported M100 (magnetic counterpart of the N100) modulation during a dichotic listening task, measured by magnetencephalography (MEG). Hillyard (1993) concluded that the enhancement of the N1 amplitude is related to endogenous neural activity elicited by attention. Johnstone et al. (2008) reported a delayed and more anterior N1 in ADHD children compared to controls while performing a Flanker task. The authors related the findings to a delayed automatic attention in children with ADHD. An interesting differentiation between endogenous and exogenous components of the N1 comes from Näätänen & Picton (1987). They discriminated between true N1 components, influenced by temporal and physical parts of the presented stimulus and other components of the N1, which are not primarily stimulus-driven, but related to the condition in which a stimulus occurs. Furthermore, the generation of "true" components was related to three brain areas: first, auditory cortex on the supratemporal plane, second lateral temporal and parietal association cortex, and third motor and premotor cortex. Other components of the N1 were supposed to be related to: first, the mismatch-negativity, second, a temporal component of the processing negativity, and third, a frontal component of the processing negativity. An important conclusion of Näätänen & Picton (1987) was that "true" N1 components are shorter in latency. Evidence for emotional modulation of N1 amplitude comes from Ehlers et al. (2006), who reported enhanced amplitude in participants with posttraumatic stress disorder (PTSD) compared to controls at frontal and temporal electrode positions, while viewing sad faces. They related their results to an elevated attentional level in processing of sad stimuli in participants with PTSD.

With respect to the present study, a group-specific modulation of the N1 component was expected especially in PG, due to differences in attentional processing of addiction-relevant cues. In the PG group especially high-risk situations and moments of winning money might function as addiction-relevant cues, which in turn track attention.

3.1.1.2 Expert-based N170

The N170 ERP component with a negative deflection around 170 ms after stimulus presentation was reported to be linked to the structural encoding of faces (Eimer, 2000). The N170 is located over lateral posterior electrode positions in the fusiform gyrus. Results from fMRI studies (Kanwisher & Yovel, 2006) strengthened the theory that a region within the fusiform gyrus functions as a face-specific processing module, called fusiform face area, reflected by the face selectivity of the N170.

However, other groups questioned the theory of a face selective N170 ERP component. Evidence came from Tanaka et al. (2001), who reported an enhancement of the N170 amplitude when experts (dog experts and bird experts) had to categorize objects in their domain of expertise compared to a categorization of objects outside their domain of expertise. The authors related the modulation of the N170 to a consequence of perceptual learning in the sense that the fusiform face area is used to process other genres of perceptual expertise besides faces. Another confirmation of the expert-specific accent of the N170 is reported from Gauthier et al. (2003), who compared car-experts to non-car-experts, while performing a dual task (deciding between cars vs. faces during interfering context). Car-experts showed a higher N170 amplitude during processing of car stimuli and a lower N170 amplitude during face processing in the context of car stimuli. Car perception interfered with competing face perception (decreased N170 amplitude during face processing in the context of car stimuli) and this interference was positively correlated with car expertise. Another evidence for an experience-based N170 comes from Scott et al. (2008). The authors report an increase of N170 amplitude after car classifying training only from pre- to post-test. The N170 modulation was absent one week after training. The N170 modulation was linked to a lower-level categorical matching process, which might be influenced by former exposure to categories or categorical learning processes.

Regarding the present experiment, PG might demonstrate an expert-specific modulation of the N170 during early stimulus processing of cards. In addition, comparing PG and OG on N170 amplitude between different conditions (high-risk, low-risk) might reveal a more detailed picture of card-gambling-expertise in PG.

3.1.1.3 Frontal selection positivity (FSP)

In everyday situations persons often need to discriminate between relevant and irrelevant stimuli to select the adequate behavior. In an experiment of Kenemans et al. (1993)

participants had to push a button if a stimulus showed a specific combination of spatial frequency and orientation or to inhibit their response if the target showed only one or none of the relevant features. While comparing frequency relevant to frequency irrelevant stimuli a FSP was reported on Fz with a latency of 150–200 ms post-stimulus. Furthermore, the authors announced selection negativity at Oz (around 200 ms) and N2b at Cz (200–250 ms). Frequency relevance initiated FSP at 160 ms followed by a further enhancement in amplitude at 180 ms, when the stimulus also had the appropriate orientation. This fact led to the conclusion, that frequency relevant processing has a higher level in hierarchy than orientation processing. Potts et al. (2008) proposed that the FSP may indicate an interaction between posterior systems of perceptual representation, which are modality-specific and modality-independent frontal systems, responsible for evaluation of appropriateness. In a study by Jonkman et al. (2004) ADHD children were compared to a control group in a visual color selection task to test for selective visual processing. Participants were asked to attend or to ignore rectangles due to a specific color. Results showed worse behavioral performance (more omissions and false alarms) and a smaller FSP (difference waves of attended minus unattended non-targets) in ADHD children than in controls, which was interpreted as an early filtering deficit. Martin & Potts (2004) compared high with low impulsive participants in a reward prediction study. Results showed, that high-impulsive participants expressed the highest FSP (in that study called P2a) amplitude after unexpected rewards and lowest amplitude, when the reward was expected, but not supplied. Source analysis of the P2a within the non-predicted reward condition revealed a main source located in the medial OFC. The authors concluded that high-impulsive participants reveal stronger susceptibility to reward signals which is accompanied by a hypersensitivity in orbitofrontal reward processing.

With respect to the present study, group-specific differences between distinct levels of perceived risk were expected. PG are expected to behave more impulsive than OG and, therefore, might be especially stimulated by an attracting high-risk situation, which should be reflected by enhanced FSP amplitude in high-risk compared to low-risk trials exclusively in PG.

3.1.1.4 N2 and conflict processing

The N2 is a negative ERP component at fronto-central electrode positions with a peak latency of around 250 ms after stimulus presentation (Yeung et al., 2004). In a study by Kopp et al. (1996) participants performed a flanker task (Eriksen & Schultz, 1979), where

they had to respond as fast as possible and as correct as possible, to a central target-stimulus. The target-stimulus (arrow with a specific direction) was surrounded by two additional stimuli, called flankers, one above and one below the centrally presented target. In the congruent condition all three arrows had the same orientation (identical). The incongruent condition consisted of flankers pointing to the opposite direction than the target stimulus. Furthermore, there was a neutral condition (squares as flankers) and all conditions had two levels of spatial frequencies (1 or 3 degrees of visual angle distance between target and flankers). Results revealed that in the incongruent flanker condition the magnitude of the erroneous responses covaried with the N2 amplitude. Kopp et al. (1996), therefore, proposed that the N2 is sensitive to the avoidance of a wrong response. Lange et al. (1998) tested selective attention to color (red or blue), location (right or left to fixation) and the conjunction of color and location while measuring EEG. The authors reported that the N2b activity reflected feature-independent selection processing, because the N2 was elicited in each condition (color, location, and conjunction selection). In addition, source analysis with BESA revealed a probable common source of the N2 in the ACC. Yang et al. (2007) associated the N2 amplitude with the amount of perceptual conflict while a recent study by Mennes et al. (2008), however, indicated that the N2 was only sensitive to the pure presence of conflict. They used a gambling paradigm, where participants had to choose between two locations (left or right) of an imaginary hidden token under a proportionally divided (two parts) color bar. Results showed similar N2 amplitudes over different levels of response conflict. Therefore, the authors concluded that the N2 seems not to be sensitive to the amount of conflict.

In the present gambling paradigm the N2 could discriminate PG and OG regarding conflict processing, especially in high-risk situations. This only holds when the N2 is indeed modulated by different levels of perceived conflict.

3.1.1.5 P 3 component

The P3 is described as the most positive peak in the time window between 250–500 ms after stimulus presentation, which can vary with modality, task conditions, and age of the subjects (Polich, 2007). The P3 component can be divided in the P3a, reflecting stimulus-driven attention with a fronto-central origin and the P3b, being associated to attention and memory processing with a parietal origin (Polich, 2007). Throughout literature the fronto-central P3 is reported as P3a, novelty P300, or no-go P300, which (Polich, 2007) took together as probable variants of the same ERP where scalp topography is modulated by

task demands and attention. The P3b is elicited by an oddball task, confronting participants with two stimuli in a random sequence, with one frequently and one infrequently occurring target (Polich & Cried, 2006). When participants were instructed to react by button-press to the infrequent target-stimulus a P3b was elicited. If an additional infrequent distractor is added to this paradigm (third stimulus, which should be ignored), which is difficult to discriminate from the target stimulus, then while refraining to respond to this distraction, a P3a can be observed. An experiment by de Bruijn et al. (2008) revealed an enhancement of the P3a while two persons performed a go/no-go task together. A comparison between two no-go conditions was accomplished: first, the no-go stimulus demanded a response inhibition of the other person as well (similar action) whereas in the second, the no-go stimulus was the target for the other person to respond to (conflicting action). The results showed more errors on conflicting actions coupled with a lower P3a amplitude compared to similar actions. Furthermore, differences in RT and P3a between the conditions were caused by the slow and unsuccessful competitors. These results clearly demonstrated the cognitive modulation of the P3a, in the sense than the amount of competition modulates the extent to which an action plan of another person is incorporated in one's own, which in turn modulates response inhibition. Polo et al. (2003) demonstrated an enhanced left frontal P3a amplitude to deviant tones in alcoholic patients compared to controls, which the authors interpreted as impaired involuntary attention in those patients.

In a study by Gomez et al. (2008) participants had to react by button press to validly (82%) and invalidly (18%) cued targets. The authors related increased P3b amplitude in invalidly cued targets relative to validly cued targets to enhanced context updating of the working memory. In addition the authors concluded that invalidly cued targets were treated as a stimulus with low probability, analogous to deviant stimuli in oddball paradigms. This is in accordance with Dunchan-Johnson & Donchin, (1977), who showed that the amplitude of the P3b at Pz electrode position was inversely proportional to the probability of task-relevant events. Kok (2001) tackled the view that the P3 amplitude is a measurement tool for intensity processing (Polich & Kok, 1995). He proposed that the P3b represents activation of elements in an event categorization network that is regulated by shared operation of attention and working memory. Iacono and colleagues (2003) supposed that a P3b amplitude reduction could function as an indicator of genetic vulnerability for externalizing spectrum disorders, like risk for substance use disorders and antisocial personality disorders, all reflected by poor inhibitory control. Yeung et al. (2004) showed in a gambling paradigm that the P300 at midline posterior scalp electrodes increased both

with the magnitude of the chosen stimuli and with the magnitude of the alternative not chosen stimuli. Participants had to choose between two cards which were coupled with monetary gains and losses. After perceiving the outcome the participants were confronted with an alternative outcome (what they would have lost or won, if they had chosen the other card). The authors concluded that the P300 codes reward magnitude, irrespectively whether the reward is indeed obtained. These results closely fit to findings of Namkoong et al. (2004), who found that the P3 amplitude is a useful neuronal correlate of alcohol craving in alcohol-dependent patients.

The hypotheses of the present experiment are that first, OG might show an enhanced P3a due to enhanced response conflict especially when they have to make a decision in high-risk situations. Second, PG might express a general lowered P3b amplitude, because of being generally desensitized to the magnitude of the received reward, or due to their poor inhibitory control (Iacono et al., 2003). Third, high-risk and win situations can function as potential addiction-cues (Namkoong et al., 2004), which are expected to enhance ERP amplitudes in the P3b time window exclusively in PG.

3.1.1.6 Late positive complex

The late positive potential (LPP) describes a positive deflection of the ERP signal in the time window between 350 and 750 ms post stimulus which has shown to be sensitive to emotional modulation (Schupp et al., 2000). The authors presented emotional pictures to participants while measuring ERPs. Results showed that emotional pictures (pleasant or unpleasant) evoked larger LPP than neutral pictures. Interestingly, within the emotional category there was an enhancement of LPP amplitude for high arousing pictures. It was concluded that context and intrinsic motivational relevance of the presented affective stimuli might play a crucial role in its LPP modulation. Research by Moser et al. (2006) extended the findings by Schupp et al. (2000) by instructing participants to view, enhance, and suppress emotional responses to emotional stimuli. Results showed smaller LPP amplitude to neutral compared to highly arousing stimuli. In addition, the LPP was modulated by the experimental instructions, in the way that an intentional suppression of responses to unpleasant and highly arousing stimuli was accompanied by a LPP amplitude reduction. The authors concluded that the LPP can be influenced by emotional regulation. Liotti et al. (2000) recorded ERP during a mixed-trial Stroop color-word paradigm. Participants had to read color words like “yellow”, or “ blue”, which were presented against a black screen. In the congruent condition the words were presented in the

congruent color ("yellow" was presented in yellow color), whereas the incongruent condition consisted of words presented in a conflicting color ("yellow" was presented in blue color). The authors reported a more extended left temporo-parietal LPP in incongruent relative to congruent color word trials. They concluded that the prolonged LPP in the incongruent condition reflected additional semantic processing of word meaning. Dolcos & Cabeza (2002) dissociated parietal and fronto-central electrode positions with respect to their sensitivity to arousal and valence in the time window between 500 and 800 ms post stimulus. While fronto-central positions were sensitive to both arousal and valence (higher amplitude for pleasant compared to unpleasant or neutral stimuli), parietal positions were only sensitive to arousal [higher amplitude for emotional (both pleasant and unpleasant) compared to neutral stimuli]. Evidence for LPP sensitivity to addiction-related cues comes from Wölfling et al. (2008), who revealed enhanced LPP in the 450-750 ms time window to cannabis-associated stimuli in heavy cannabis users compared to healthy controls. Within the cannabis group LPP amplitude was higher for cannabis-associated stimuli compared to alcohol-associated or neutral stimuli. The authors related the LPP modulation to the emotional relevance of addiction-related stimuli. This is in line with results from Franken et al. (2004), who demonstrated LPP enhancement to cocaine-related cues compared to neutral pictures in cocaine addicted persons.

Regarding the hypotheses of the present experiment, especially high-risk situations might lead to an enhancement of arousal in PG, which should be reflected by a higher LPP amplitude.

3.1.1.7 Feedback-related negativity

Feedback-related negativity (FRN) refers to a negative deflection in the ERP with a peak around 250 ms after presentation of feedback (Hirsh & Inzlicht, 2008). Miltner et al. (1997) reported a negative ERP component following a negative feedback with a peak latency between 230 and 330 ms with a duration of 260 ms, which was largest on midline electrodes. Participants performed a time estimation task, where they had to estimate the duration of one second by button press. Feedback was given 600 ms after response in three different modalities (visual, auditory, and somatosensory) indicating the correctness of participants' decisions (per modality one feedback for correct and one for incorrect responses). Feedback following incorrect performance elicited FRN with probable regional sources in the ACC or the supplementary motor area. Holroyd and Coles (2002) interpreted the results of Miltner et al. (1997) in the way that the FRN might reflect error detection or

benefitting from error information to prevent repeated errors in the future. In a study of Hajcak et al. (2007) FRN amplitude was modulated by reward probability, in cases when participants' expectations were considered (only when predictions were made after participants' gambling choice). Bellebaum & Daum (2008) further explored the relationship between FRN amplitude and the magnitude of negative prediction errors, inferring reward expectation directly from the choice behavior of the participants. Participants had to choose between two boxes, with one box holding a higher reward probability (2/3) than the other (1/3). After participants had learned the rule, it was shown that after a 2/3 choice the difference in FRN amplitude between non-reward and reward was higher compared to a 1/3 choice. The authors interpreted the results in the way that the FRN is sensitive to the magnitude of the negative prediction error, which was higher when the negative feedback had a lower chance of occurrence. Source analysis confirmed the ACC to play a crucial role in coding negative reward prediction errors. With respect to a personality traits, results from Hirsh & Inzlicht (2008) demonstrated that the degree of neuroticism modulated FRN amplitude exclusively after uncertain feedback in a time estimation task (Miltner et al., 1997). More specifically, high neurotic persons indicated lower FRN to negative feedback than to uncertain feedback, leading to the interpretation that high neurotic participants prefer clear but negative feedback than bearing the inconvenience of uncertainty.

Referring to the present experiment losing money compared to winning money might modulate FRN in both PG and OG, because negative feedback is given. In addition, PG may differ in the amount of reward expectation from OG as PG have shown a reduced sensitivity of the reward system (Reuter et al., 2005), which could be expressed in FRN amplitude differences between the groups after win trials.

3.1.2 Hypotheses and goals of the EEG study

The present EEG study was the first one, at this time point, comparing PG and OG with respect to both risk assessment and reward processing using an ecologically valid paradigm. ERPs and source models should reveal spatio-temporal processing in PG and OG in more detail. Based on the above-mentioned studies the following hypotheses were proved:

1) During risk assessment it was expected that general enhanced processing of gambling-related material should strengthen early modulations in attentional (N1) or expert-specific (N170) processing in PG. These effects could vary between different levels of perceived risk. In addition, in a later time window frontal selection potentials and conflict processing (N2, P3a) might differ between groups. Furthermore, group-specific differences in risk assessment were expected which should be accompanied by centro-parietal P3b and LPP amplitude modulation.

2) During reward processing, valence-related differences in ERP components were assumed. First, error processing, reflected in the fronto-central FRN component might differ between PG and OG due to differences in reward expectation. Second, later components might show enhanced amplitude in the P3b time window at centro-parietal locations especially in PG due to higher arousal while winning money.

3) FMRI constrained source analyses will integrate the results of both studies to give a description for the temporal sequence of regional brain activity underlying PGG behavior separately for risk assessment and reward processing.

3.2 Methods - EEG study

3.2.1 Study participants

The EEG study group consisted of 12 healthy male OG (mean age 35.8 ± 9.5 years; range 22 – 50 years) and 12 male PG (mean age 33.8 ± 7.8 years; range 23 - 43 years). All participants were right handed, except for one ambidexter in the PG group, according to the Edinburgh Handedness Questionnaire (Oldfield, 1971). Both groups did not differ in age ($F_{[1,22]}$=0.32, p=0.6) and smoking behavior (z=-1.48, p=0.3). As in experiment 1 it was decided to investigate only male participants, as the prevalence of PGG in men is reported to be two times higher than in women (Grant & Potenza, 2004). Participants were recruited through advertisements and were familiarized with the gambling environment in the laboratory. Prior to enrollment into the study, all participants underwent a structured psychiatric interview. OG did not report a history of psychiatric or neurological illness or regular drug use and were not under current medication. In the PG group, four participants were presented with a diagnosis of problem gambling (3 or 4 criteria; Toce-Gerstein et al., 2003) and eight participants had a diagnosis of PGG (≥ 5 criteria) according to DSM IV (see appendix A 6). Again, all individuals were assessed with the KFG questionnaire (Petry, 1996; see appendix A 7). All PG scored between 19 and 51 points (mean 33.4 ± 10.9; threshold for PGG is set at 16 points), whereas OG scored between 0 and 10 points (mean 3.8 ± 3.1). In addition, all participants were evaluated with a German version of the SOGS (see appendix A 8; Lesieur & Blume, 1987). Participants who scored ≥ 5 points were classified as “probable pathological gamblers”. All PG scored ≥ 5 on the SOGS (mean 9.7 ± 3.8); OG: ≤ 2 (mean 0.9 ± 0.8). The study protocol was designed according to the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1984) and was approved by the local ethics committee of the University of Bremen. All participants were informed about the procedure and gave written informed consent to participate.

3.2.2 Data protection, data security and legal framework

The study protocol was designed according to the Code of Ethics of the World Medical Association (Rickham, 1964) and was approved by the local ethics committee. All participants were informed about data collection, data protection and data security, and gave written informed consent to participate prior to the EEG measurement (see appendix A 5). In addition, participants were also informed about the EEG method and about their right to quit the experiment at any time without giving reasons (see appendix A 4). Furthermore, participants were naïve to the experimental design and the working hypotheses of the current study.

3.2.3 Experimental design

The stimulus material and trial specifications were the same as in experiment 1 (see Figure 2.1).

3.2.4 EEG data acquisition

EEG data were recorded from 64 Ag-AgCl scalp electrodes (see Figure 3.1) placed according to the extended internationally standardized 10/20 system. The EEG signal was amplified (REFA multi-channel system; TMS international) and digitized with a sampling rate of 512 Hz (band-pass filter 0,1 – 155 Hz; average referenced). Impedance per channel was kept below 15 kΩ. Vertical and horizontal electrooculographic (EOG) recordings were obtained from four additional Ag-AgCl surface electrodes (above and below the right eye; lateral to both eyes). Individual head electrode positions were digitized with Zebris Motion Analyzer System (CMS 20; Zebris Medical GmbH).

3.2.5 EEG data analysis

BESA® software (version 5.1.8.10; MEGIS Software GmbH; Munich Germany) was used to analyze EEG data. Artifacts were detected with the artifact scan tool implemented in BESA®, where sweeps at every channel with amplitudes above 100µV were rejected for averaging. Additionally, single individual data was visually inspected for artifacts and channels were interpolated if necessary (the number of interpolated channels was kept below 4). Individual blinks of each participant were averaged with a template-based

method (Ille et al., 2002) to create an artifact topography per participant (averaged blink epochs over all subjects). Artifact topographies served as spatial components for single and grand average analyses. For stimulus-locked analyses data were averaged over 500 ms pre to 1500 ms post stimulus onset. ERP-data were baseline-corrected to the mean amplitude of the 100 ms pre-stimulus period. After averaging a low-pass filter of 30 Hz was applied and evoked potentials were visually inspected, and exact margins of the predefined time windows (latency ranges of the ERPs used in prior ERP studies related to the topic of this experiment) were designated for further analysis.

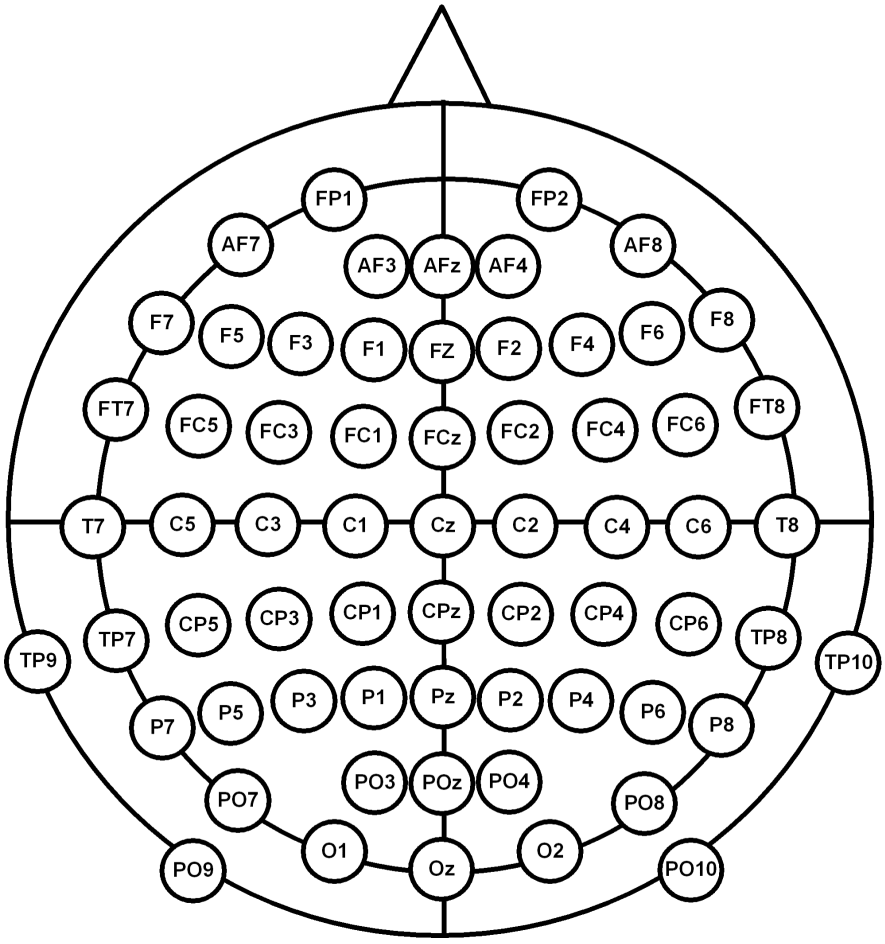

Figure 3.1. 64-channel electrode setup applied in the present study.

After grand averaging, the ERP data were visually inspected and time windows were defined based on both peaks of deflections and a priori set hypotheses. For the phase of risk assessment/start of the game P3b (400±20 ms) and LPP (600-800 ms), as well as for the reward processing phase/end of the game N1 (125±25 ms) and P3b (390-440 ms) were included for statistical analysis. ERPs were quantified by calculating mean amplitudes stimulus locked to the start of the game (Figure 2.1; frame 3) in two time intervals (380-420 and 600-800 ms). Additionally, mean amplitudes were obtained in the same

manner relative to the moment of winning or losing (Figure 2.1; frame 4 or frame 5 dependent of the drawing behavior of the participants) in two time intervals (100-150 and 390-440 ms). Topographical analyses of mean amplitude values were performed separately for each ERP time interval including 15 approximately equidistant distributed electrodes (F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4 and P8) (cp. Fehr et al., 2006). For the start of the game, a four-way GLM repeated measures ANOVA was calculated, all including the within-subject factors ANTERIOR-POSTERIOR (AP 3 levels: frontal, central, and posterior electrode positions)**,** LATERALITY (LAT 5 levels: from right to left scalp electrode sites), RISK (high-risk, low-risk) and the between subject factor GROUP (PG, OG). Analyzing the ERP time interval for winning/losing situations was also performed applying a four-way repeated measures ANOVA including the within-subject factors ANTERIOR-POSTERIOR (AP 3 levels: frontal, central, and posterior electrode positions), LATERALITY (LAT 5 levels: from right to left scalp electrode sites), REWARD (win, lose) and the between subject factor GROUP (PG, OG). Main effects and significant interactions were adjusted according to Greenhouse Geisser (GG) where appropriate. Significant four-way interactions legitimated exploration of single electrodes by paired-sample t-tests. Two-way interactions including the factors GROUP and REWARD or three-way interaction effects including the factors GROUP, REWARD and ANTERIOR-POSTERIOR or LATERALITY were further explored with ANOVAs for each single electrode site. In case of significance ($p<.05$) or trend ($p<.1$), post-hoc analyses (paired sample t-tests) were calculated.

3.2.6 Source localization method

Source localization was calculated for the above specified time windows (see second paragraph of chapter 3.2.5) using sLORETA method (standardized Low Resolution Electromagnetic Tomography; Pascual-Marqui et al., 2002; http://www.unizh.ch/keyinst/NewLORETA/LORETA01.htm). The algorithm of sLORETA uses a three-shell spherical head model registered to standardized stereotactic space (Talairach & Tournoux, 1988) and rendered to the Montreal Neurological Institute (MNI) template brain. The MNI template brain includes 6239 voxels (5 mm resolution), while each voxel contains an equivalent current dipole. At each voxel, sLORETA calculates the three-dimensional distribution of electrically equivalent active neuronal generators in the brain as a current density value (Ampere per square meters; A/m^2). An important constraint of the sLORETA linear solution is that the generator activity of any

given voxel has to be as similar as possible to the average activity of its surrounding voxels, dealing with the assumption of highly synchronicity of neighboring neurons. In addition sLORETA has no assumptions about the amount and the location of sources (Esslen et al., 2004).

3.2.7 fMRI constrained source analysis – Model forming

Source waveforms were calculated using a four-shell spherical head model, which considered characteristics of the individual brain like, conductance, bone, cerebrospinal fluid, and scalp (Scherg & Berg, 1996), and a regularization constant of 1 percent for the inverse operator to reduce the interaction between sources. Two separate source models were created for each the start of the game and for the end of the game. Regional sources (RS) were seeded for the start of the game following fMRI activation foci revealed by the contrast (high-risk PG > low-risk PG) > (high-risk OG > low-risk OG); respectively (win PG > lose PG) > (win OG > lose OG) for the end of the game. A RS consists of three equivalent current dipoles with identical location but reciprocally orthogonal orientations (Scherg & Berg, 1996; Scherg & von Cramon, 1986). The fact that the activity of RS is hardly sensitive to small differences between the modeled location of active brain regions and individual anatomical location (Scherg & Berg, 1996; Scherg & Picton, 1991), the obtained source waveforms for the fMRI seeded sources were robust despite anatomical differences between participants of experiment 1 (fMRI) and experiment 2 (EEG).

For the start of the game a multiple source model on group differences (PG vs. OG) of ERP difference waves (high-risk vs. low-risk) was calculated. For the end of the game the multiple source model was calculated on group differences (PG vs. OG) of ERP difference waves (win vs. lose). The fMRI contrast for the start of the game [(high-risk PG > low-risk PG) > (high-risk OG > low-risk OG)] resulted in three activation foci seeded as RS (see Table 3.1), which were fixed according to their location in the source model. Furthermore, the fMRI contrast for the end of the game [(win PG > lose PG) > (win OG > lose OG)] yielded three activation foci seeded as RS (see Table 3.2), which were also fixed according to their location in the source model. To avoid reciprocal interaction, so-called “crosstalk” between sources with a distance of less than 30 mm, they were averaged according to the nearest neighbor method (Bledowski et al., 2006). This was necessary for the two parietal sources at the end of the game, where the coordinates of the two sources were averaged. The new averaged source (see Table 3.2, RS 2) was located within the two centimeter range from its original fMRI peak locations. The averaging of the coordinates of

neighboring sources is justified by the integrative nature of RS in a multiple discrete source model. The reason is that errors in the corresponding center location smaller than two centimeters do not sufficiently influence source waveforms, as long as the distances between the different sources are larger (Bledowski et al., 2006; Scherg & Berg, 1991).
Additionally to the three fixed RS, a sequential fitting procedure was applied in BESA for the start of the game to reduce residual variance of the model. Three discrete time windows were defined after visual inspection of the global field power (GFP) and signal time course. For the 80-160 ms time window two sources, RS 4 and RS 5, were fitted. In the 360-430 ms time window, again two sources, RS 6 and RS 7, were fitted, while RS 4 and RS 5 were switched off. Furthermore, for the 500-940 ms time window two additional sources were fitted, RS 8 and RS 9, while RS 4-7 were switched off. The model for the start of the game, therefore, consisted of 9 RS and explained a variance of 93.4 percent (see Table 3.1 and Figure 3.7).

Table 3.1 Talairach peak coordinates (x, y, z) of significant fMRI activation clusters for the group (PG vs. OG) x risk (high-risk > low-risk) interaction (upper part) and additionally fitted regional sources (RS) for the start of the game (lower part); L = left; R = right.

start of the game				
contrast activity	**(x, y, z)**	**fMRI RS**	**brain region**	**(x, y, z)**
R superior temporal gyrus	(67, -25, 1)	RS1	R superior temporal gyrus	(67, -25, 1)
R inferior frontal gyrus	(46, 42, -5)	RS2	R inferior frontal gyrus	(46, 42, -5)
R thalamus	(10, -33, 3)	RS3	R thalamus	(10, -33, 3)
		additional RS		
		RS4	L orbitofrontal gyrus	(-40, 51, -8)
		RS5	L middle temporal gyrus	(-49, -28, -9)
		RS6	R superior parietal lobe	(34, -58, 57)
		RS7	L superior frontal gyrus	(-30, 52, 34)
		RS8	L inferior frontal gyrus	(-54, 26, 15)
		RS9	R postcentral gyrus	(49, -29, 58)

For the end of the game, additional to the two fixed RS, a sequential fitting procedure to reduce residual variance was performed. Two discrete time windows were determined again after visual inspection of the GFP and signal time course. For the 80-160 ms time window, RS 3-5 were additionally fitted, and for the 200-1000 ms time window, RS 6-11 were fitted, while RS 3-5 were switched off. The model for the end of the game included 11 RS which explained 95.2 % of variance (see Table 3.2 and Figure 3.9).

Table 3.2 Talairach peak coordinates (x, y, z) of significant fMRI activation clusters for the group (PG vs. OG) x reward (win > lose) interaction (upper part) and additionally fitted regional sources (RS) for the end of the game; L = left; R = right.

end of the game				
contrast activity	**(x, y, z)**	**fMRI RS**	**brain region**	**(x, y, z)**
R superior frontal gyrus	(24, 15, 56)	RS1	R superior frontal gyrus	(24, 15, 56)
L inferior parietal lobe	(-32, -55, 44)	RS2	L superior parietal lobe	(-30, -52, 50)
L superior parietal lobe	(-28, -50, 55)			
		additional RS		
		RS3	L anterior cingulate gyrus	(-14, 22, -4)
		RS4	R inferior frontal gyrus	(60, 35, -10)
		RS5	R superior parietal lobe	(34, -51, 52)
		RS6	L inferior frontal gyrus	(-61, 36, 1)
		RS7	R middle frontal gyrus	(54, 40, 16)
		RS8	L cerebellum	(-47, -79, -41)
		RS9	R supramarginal gyrus	(67, -54, 30)
		RS10	L superior frontal gyrus	(-14, 72, 7)
		RS11	R lingual gyrus	(22, -77, 0)

3.2.8 fMRI constrained source analysis – Data analysis

The obtained source models were applied on single individual data [difference waves for the difference between high-risk and low-risk (start of the game) and for the difference between win and lose (end of the game)]. The root mean square [RMS; the square root of the mean of the added and squared power (in nano-Ampere per meter; nA/m) of three orthogonally oriented equivalent current dipoles at the same location] of each RS was calculated. To examine the spatio-temporal dynamics of all RS, RMS values for 50 ms time windows for each RS and each study participant were calculated (see Figure 3.8 in chapter 3.3.4.1).

GLM repeated measures ANOVAs on RMS values were performed separately for the start and the end of the game for each 50 ms time window including within-subjects factor REGIONAL SOURCE (RS: 9 levels for the start of the game; 11 levels for the end of the game) and the between-subject factor GROUP (PG, OG). The main effects and significant interactions were Greenhouse Geisser (GG) adjusted where appropriate. Post-hoc analyses (paired sample t-tests) were performed according to significant main effects ($p<.05$) and statistical trends ($p<.1$).

3.3 Results - EEG study

3.3.1 Behavioral data

RT and decision behavior (hit vs. stand) in PG and OG did not differ significantly. A repeated measures ANOVA for RTs including factors GROUP (PG vs. OG) x RISK (high-risk vs. low-risk) did not show any significant GROUP-related main effects ($F_{[1,22]}$=0.93; p=0.3; PG: low-risk: 1659±701 ms, high-risk: 2179±797 ms; OG: low-risk 1497±611 ms, high-risk: 1819±577 ms), and GROUP x RISK interaction ($F_{[1,22]}$=2.81; p=0.1). Both groups showed significantly longer RTs in high-risk compared to low-risk conditions (main effect of the factor RISK; 1999±705 ms vs. 1578±648 ms; $F_{[1,22]=}$50.86 p<.001). Frequency of gambling was significantly higher in PG compared to OG (PG: mean: > 3 times / week; OG: mean: ≤ 3 times / month; z=-4.5, p < .01).

In addition, PG and OG did not differ in decision behavior. A repeated measures ANOVA for decision behavior with the factors group (PG vs. OG) x decision behavior (percent high-risk hit vs. percent low-risk hit) revealed no significant main effect of group ($F_{[1,22]}$=1.46; p=0.2.), and group x decision behavior interaction ($F_{[1,22]}$=1.41; p=0.2). Both groups showed significantly lower percentage of high-risk compared to low-risk hit trials (main effect of the factor decision behavior; $F_{[1,22]=}$57.2, p<0.001; PG low-risk: 97.0±5.7 percent, high-risk: 52.2±27.9 percent, OG low-risk: 97.2±7.1 percent, high-risk: 64.5±20.3 percent).

3.3.2 ERP data

3.3.2.1 ERP results – Risk assessment

A four-way interaction (AP x LAT x RISK x GROUP) was not significant in any time window of interest.

For the 380-420 ms time window a three-way interaction (AP x RISK x GROUP), ($F_{[1.6,45.0]}$=3.83, p=.041, GG-corrected) was significant, whereas (LAT x RISK x GROUP; $F_{[2.2,48.0]}$=3.05, p=.052, GG-corrected) did not reach significance but showed a statistical trend. Post-hoc tests indicated significantly lower mean amplitude values (difference: high-risk vs. low-risk) in PG compared to OG at F7 and T7, and significantly higher mean amplitude values (difference: high-risk vs. low-risk) in PG compared to OG at Pz and P4 (see Figure 3.2 and Figure 3.3).

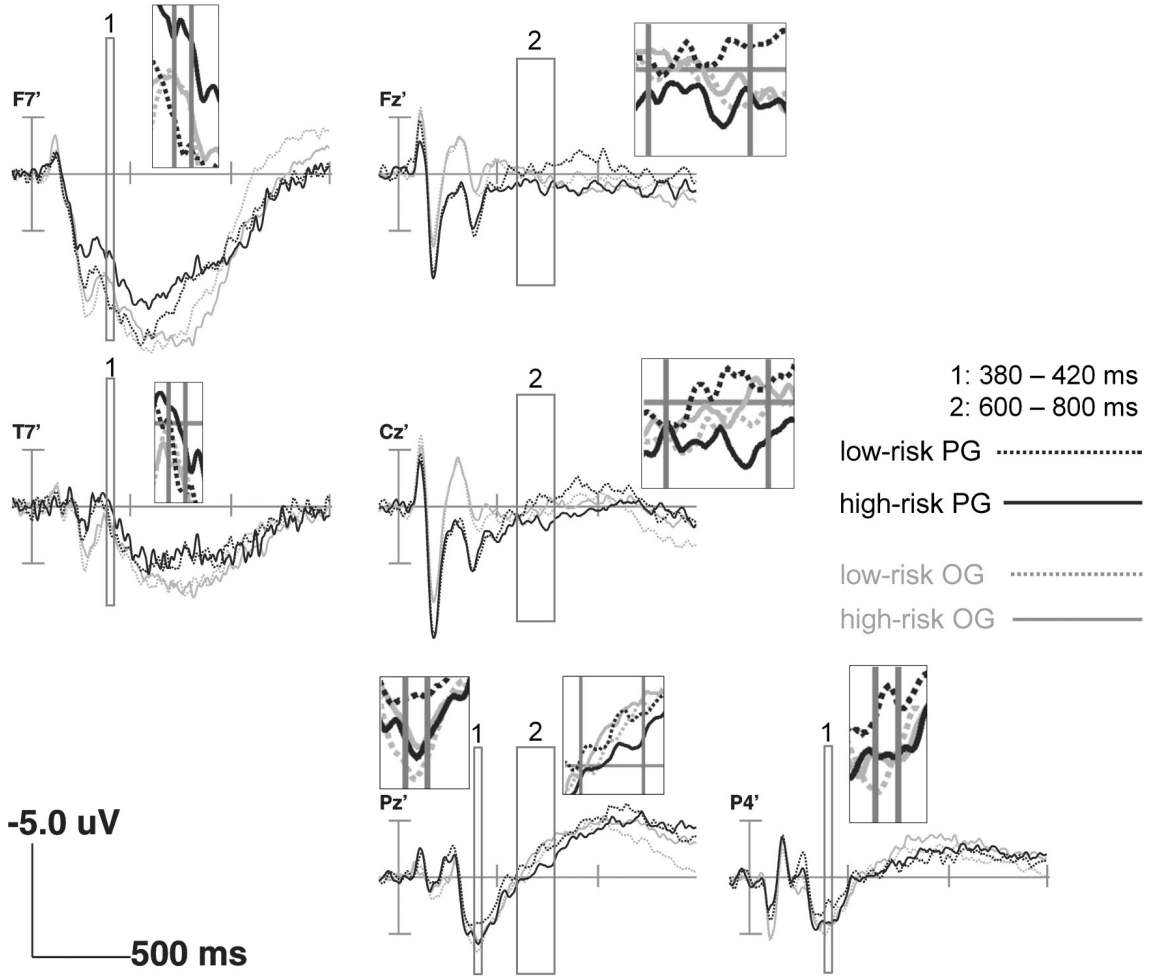

Figure 3.2 ERPs for high-risk and low-risk conditions for PG and OG for selected frontal, temporal, and parietal electrode sites. Gray boxes indicate the time windows showing significant post-hoc test results between conditions.

For the late latency time window (600-800ms) there was a significant LAT x RISK x GROUP interaction, ($F_{[2.2,47.2]}$=3.89, p=.025, GG-corrected). Post-hoc tests indicated significantly higher mean amplitude values (difference: high-risk vs. low-risk) in PG compared to OG at midline electrodes Fz, Cz, and Pz (see Figure 3.2,Figure 3.3).

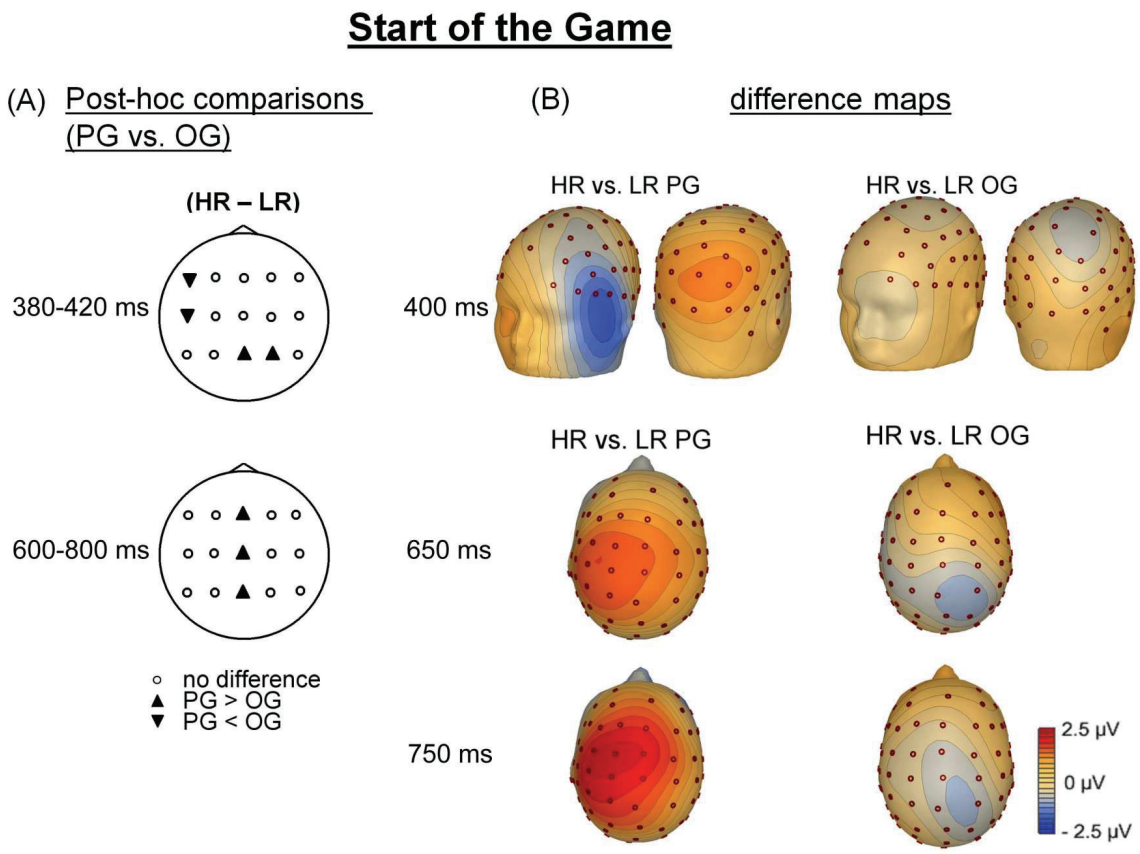

Figure 3.3 Start of the game: (A) Significant differences of mean amplitudes in microvolt (µV): Post-hoc comparisons between groups (PG and OG) for 15 electrode positions between high-risk (HR) and low-risk (LR) conditions in two time windows. Symbols in the underline represent the direction of significant differences (paired sample t-tests, p<.05). (B) Spherical spline maps (EEG-voltage, 0.25µV/step) displaying difference maps for HR vs. LR condition per group for three selected time points (400, 650, and 750 ms).

3.3.2.2 ERP results – Reward processing

A four-way interaction (AP x LAT x REWARD x GROUP) did not reach significance at any time window of interest.

For the 100-150 ms time window there was a statistical trend for a three-way interaction (LAT x REWARD x GROUP; $F_{[2.0,45.0]}=3.17$, p=.08, GG-corrected). Post-hoc tests indicated significantly higher mean amplitude values (difference: win vs. lose) in OG compared to PG at electrodes F3, Fz, and Cz (see Figure 3.4 and Figure 3.5).

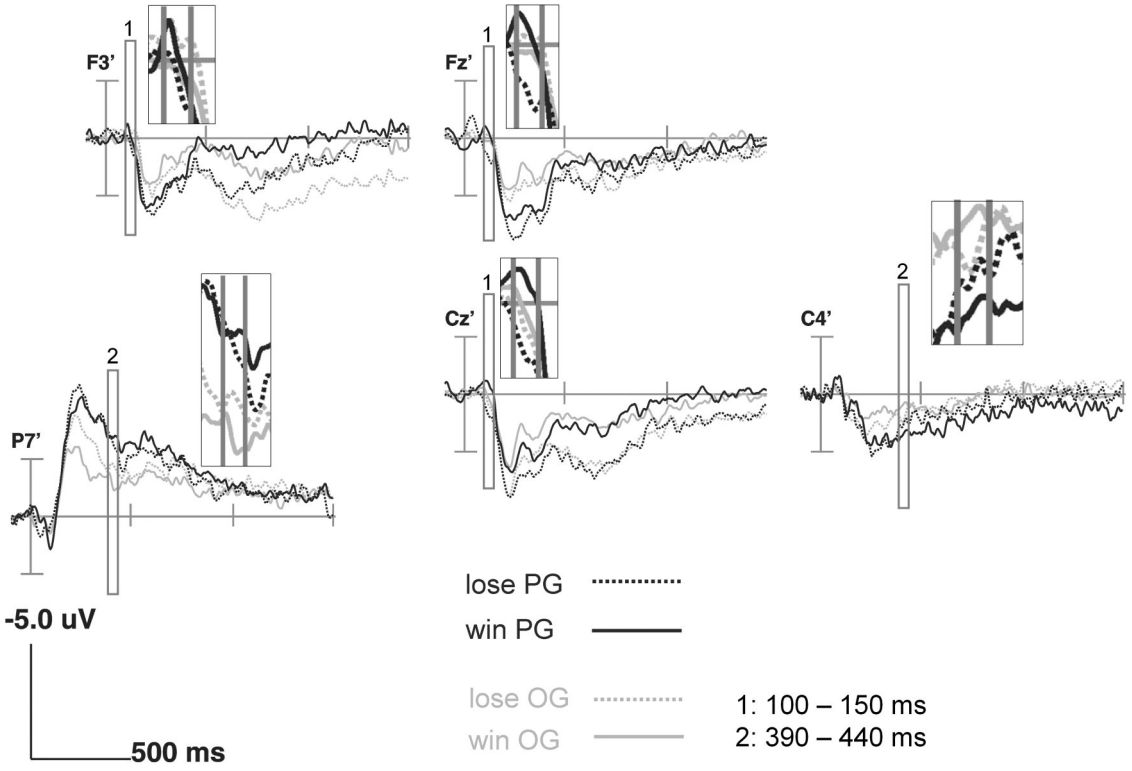

Figure 3.4 ERPs for win and lose conditions for PG and OG for selected frontal, central, and parietal electrode sites. Gray boxes indicate the time window showing significant t-tests among conditions.

For the time window 390-440 ms a three-way interaction (AP x REWARD x GROUP; $F_{[1.3,29.0]}$=2.99, p=.085, GG-corrected) revealed a statistical trend. Applied post-hoc tests indicated significantly lower mean amplitude values (difference: win vs. lose) in PG compared to OG at electrodes P7, and higher amplitude values (difference: win vs. lose) in PG compared to OG at C4 electrode (see Figure 3.4 and Figure 3.5).

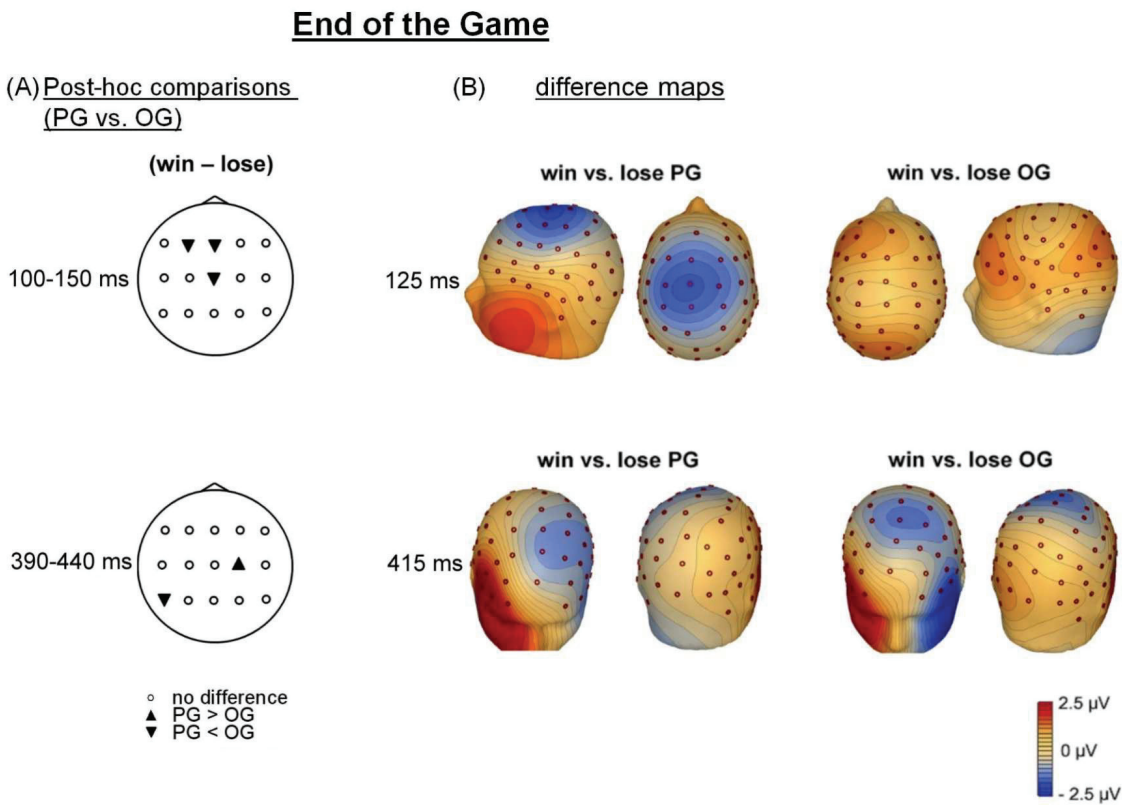

Figure 3.5 End of the game: (A) Significant differences of mean amplitude values in microvolt (µV): Post-hoc comparisons between groups (PG and OG) for 15 electrode positions between win and lose conditions for two time windows. Symbols in the underline represent the direction of significant differences (paired sample t-tests, p<.05). (B) Spherical spline maps (EEG-voltage, reference free, 0.25µV/step) displaying difference maps for the win vs. lose condition per group for two selected time points (125ms, 415ms).

3.3.3 Source localization

Analysis applying sLORETA during the start of the game (high-risk vs. low-risk conditions) indicated group-specific generator activity for the P300 time window (380-420 ms) in left and right frontal regions, and in left temporal regions for the late (600-800 ms) time window (see Figure 3.6 left panel and Table 3.3 upper part).

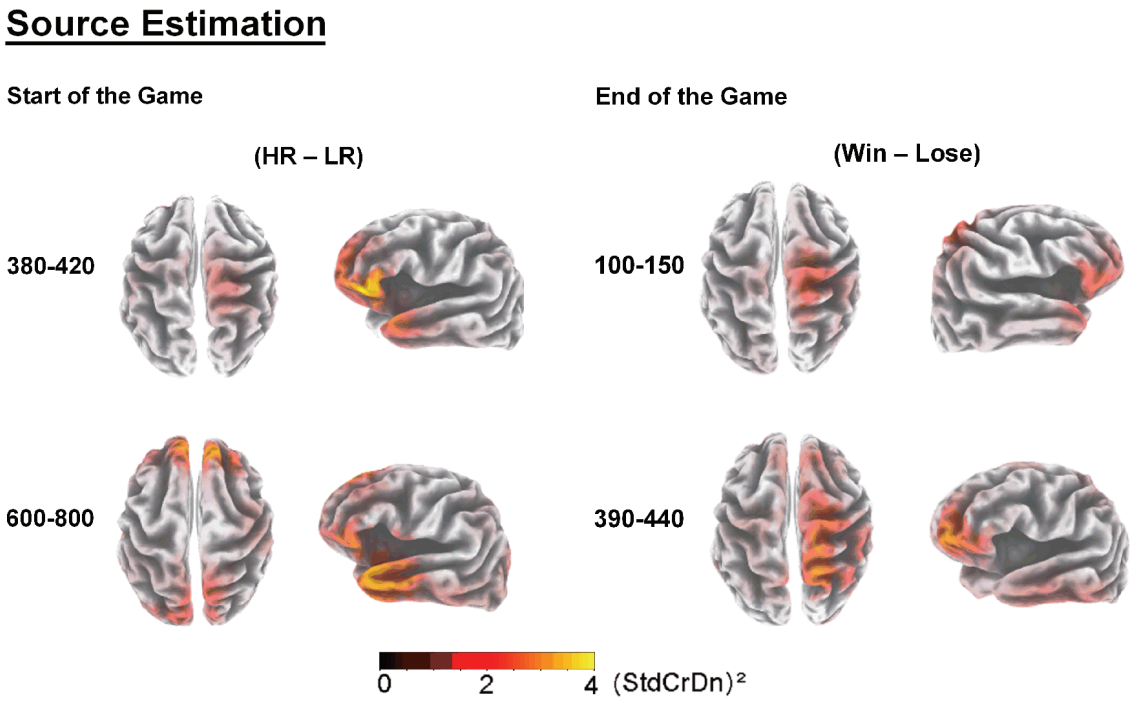

Figure 3.6 Start (left panel) and end (right panel) of the game: sLORETA-based statistical non-parametric maps for the comparison (PG vs. OG), based on difference ERPs between conditions (shown in brackets) rendered on both hemispheres (top view with anterior up or lateral view). Squared standardized current density [(StdCrDn)²] was rendered on a standard brain surface.

The end of the game (win vs. lose) revealed group-specific source activity in the 100-150 ms time window primarily in right middle frontal [Brodmann area (BA) 11], orbitofrontal (BA 47), and post-central (BA 5) regions. Furthermore, in the 390-440 ms time window estimated source activity was found at left superior frontal (BA 10) and right superior parietal (BA 7) locations (see Figure 3.6 right side and Table 3.3 lower part).

Summarizing, group differences (PG vs. OG) in risk-assessment were reflected by enhanced P300 amplitude (380–420 ms time window) at Pz electrode in PG, especially in high-risk trials compared to low-risk trials, whereas OG showed the opposite pattern. This was combined with a reduced left-frontal negativity at electrode F7 in PG in high-risk compared to low-risk situations, while OG did not demonstrate risk-specific amplitude modulation in this time window. Source estimations via sLORETA located these effects to middle frontal and orbitofrontal regions. Furthermore, in a later time window (600-800 ms) there was an increased central positivity for high-risk in contrast to low-risk trials exclusively in PG, related to source activity predominantly located in superior frontal cortex.

Table 3.3 Talairach coordinates (x, y, z) and Brodmann areas (BA) of local peaks of squared standardized current density [(StdCrDn)²] estimations for the comparison (PG vs. OG), based on difference ERPs between high-risk and low-risk conditions (start of the game), and win and lose conditions (end of the game); R=right, L=left.

Time window (ms)	Region	R/L BA	(x, y, z)
Start of the game			
380-420	middle frontal gyrus	L 11	(-45, 43, -15)
	orbitofrontal gyrus	L 47	(-50, 43, -11)
600-800	middle temporal gyrus	L 21	(-54, 9, -21)
	superior frontal gyrus	R 8	(15, 46, 44)
End of the game			
100-150	middle frontal gyrus	R 11	(45, 43, -15)
	orbitofrontal gyrus	R 47	(50, 43, -11)
	postcentral gyrus	R 5	(25, -40, 67)
390-440	superior frontal gyrus	L 10	(-25, 63, -7)
	superior parietal lobe	R 7	(15, -60, 63)

Reward processing during the end of the game produced higher fronto-central negativity after winning compared to losing money at early latencies (100-150 ms) only in PG, located in middle frontal, orbitofrontal, and postcentral brain regions. In a later time window (390-440 ms) there was enhanced negativity during win compared to lose situations in PG at left parietal electrode position (P7), whereas OG showed the opposite pattern. This ERP-effect was not reflected in sLORETA generator estimations. Additionally, PG showed different ERP activation patterns during win compared to lose situations at right central electrode positions (C4), located in superior parietal and superior frontal brain regions.

3.3.4 fMRI constrained source analysis results

Statistical parameters of repeated measures ANOVAs including the within subject factor RS and the between subject factor GROUP for 20 different time windows (50 ms blocks between 0 and 1000 ms) are listed in appendix T 1 for the start of the game and in appendix T 2 for the end of the game. Seeded RS based on corresponding fMRI analyses and additionally fitted RS are illustrated in Figure 3.7 for the start of the game and in Figure 3.9 for the end of the game. Figure 3.7 and Figure 3.9 display (A) group differences (PG vs. OG) of ERP difference waves (start of the game: high-risk vs. low-risk; end of the

game: win vs. lose), (B) global field power and residual variance (R.V.) according to the applied source model, and (C) a two-dimensional illustration of fitted and seeded sources of each model. Significant and trend to significant post-hoc comparisons are shown in Figure 3.8 for the start of the game (upper part) and for the end of the game (lower part) in 50 ms time windows.

3.3.4.1 Source analysis – Risk assessment

The source model for the start of the game (see Figure 3.7) comprised of right superior temporal, right inferior frontal and right thalamic sources derived from the fMRI contrast. Sequential fitting procedure revealed for the 80-160 ms time window additional left orbitofrontal and left middle temporal sources. In the 360-430 ms time window the fitting procedure additionally revealed right superior parietal and left superior frontal sources. For the late time window of 500-940 ms source fitting resulted in further left inferior frontal and right post-central sources. Significant main effects between OG and PG and significant GROUP x RS interactions (see appendix T 1), descriptive statistics and significant post-hoc comparisons (see appendix T 3), as well as RMS source waveforms between 0-999 ms (see appendix A 17) are illustrated and listed in detail in the appendix.

PG demonstrated larger source moments than OG in the high-risk vs. low-risk comparison within the first 100 ms at left middle temporal and right and left inferior frontal locations (see Figure 3.8, upper part), followed by differences in left inferior (250-300 ms) and left superior frontal regions (250-300 and 350-400 ms). Furthermore, PG showed larger source strength compared to OG at 550-600 ms at left middle temporal locations, which occurred parallel to sustained differences in left orbitofrontal (550-750 ms), superior frontal (550-750 ms), and right inferior frontal (600-700 ms) regions. In addition, PG showed increased source strength compared to OG in the thalamus (in the 650-950 ms time window - with an exception for the 800-850 ms time window) and in the left superior frontal cortex (850-950 ms).

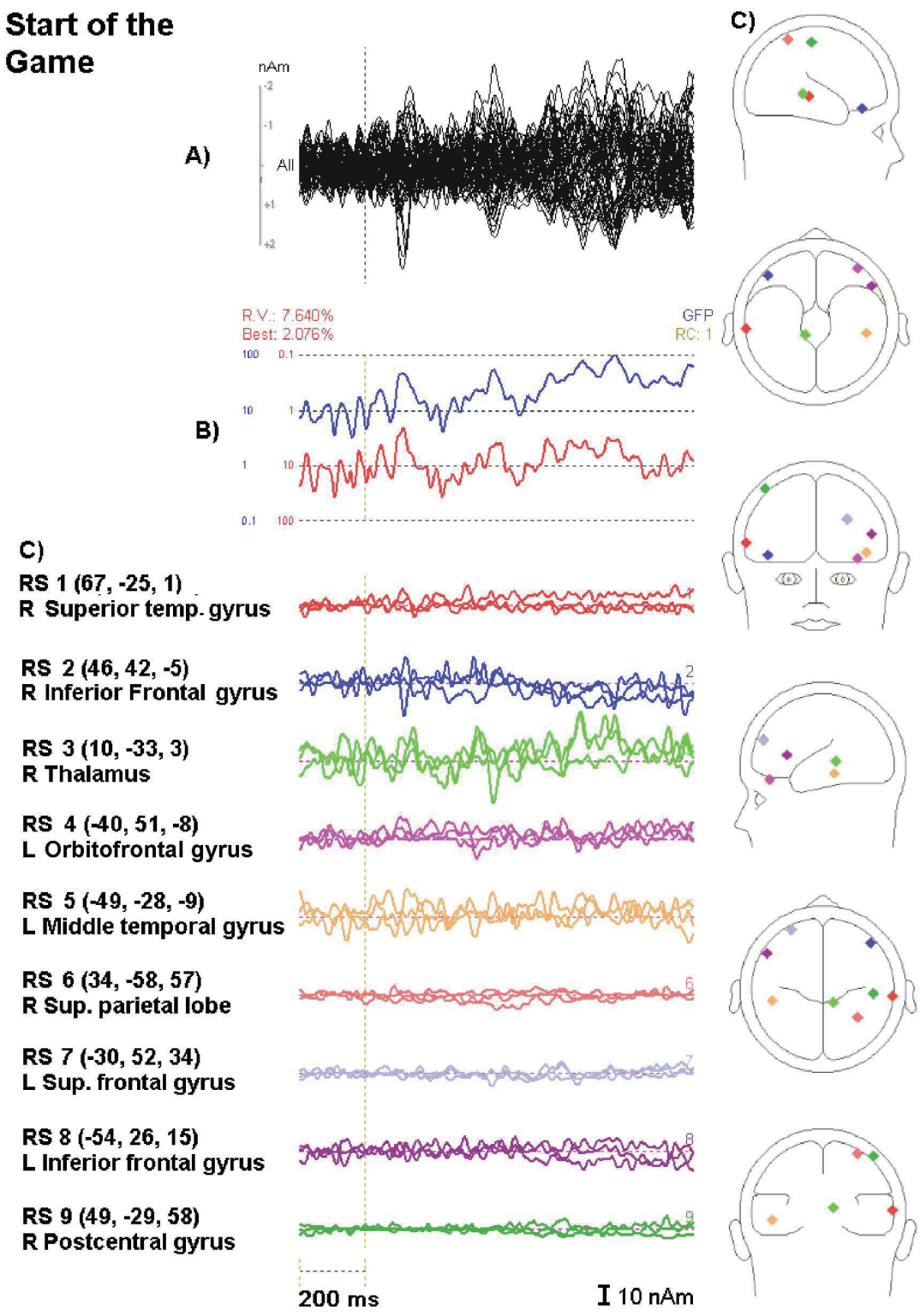

Figure 3.7 Source model for the start of the game: (A) Electrode overlay plot of the high-risk vs. low-risk difference wave for PG minus OG (-200-1000 ms); (B) Global field power (GFP; blue curve) and residual variance [(RV) and best fit; red curve]; (C) Regional sources (RS) with Talairach coordinates and scalp location (L=left; R=right). Regional sources 1-3 were seeded according corresponding fMRI peak activations – RS 4 to 9 were added by sequential fitting procedures.

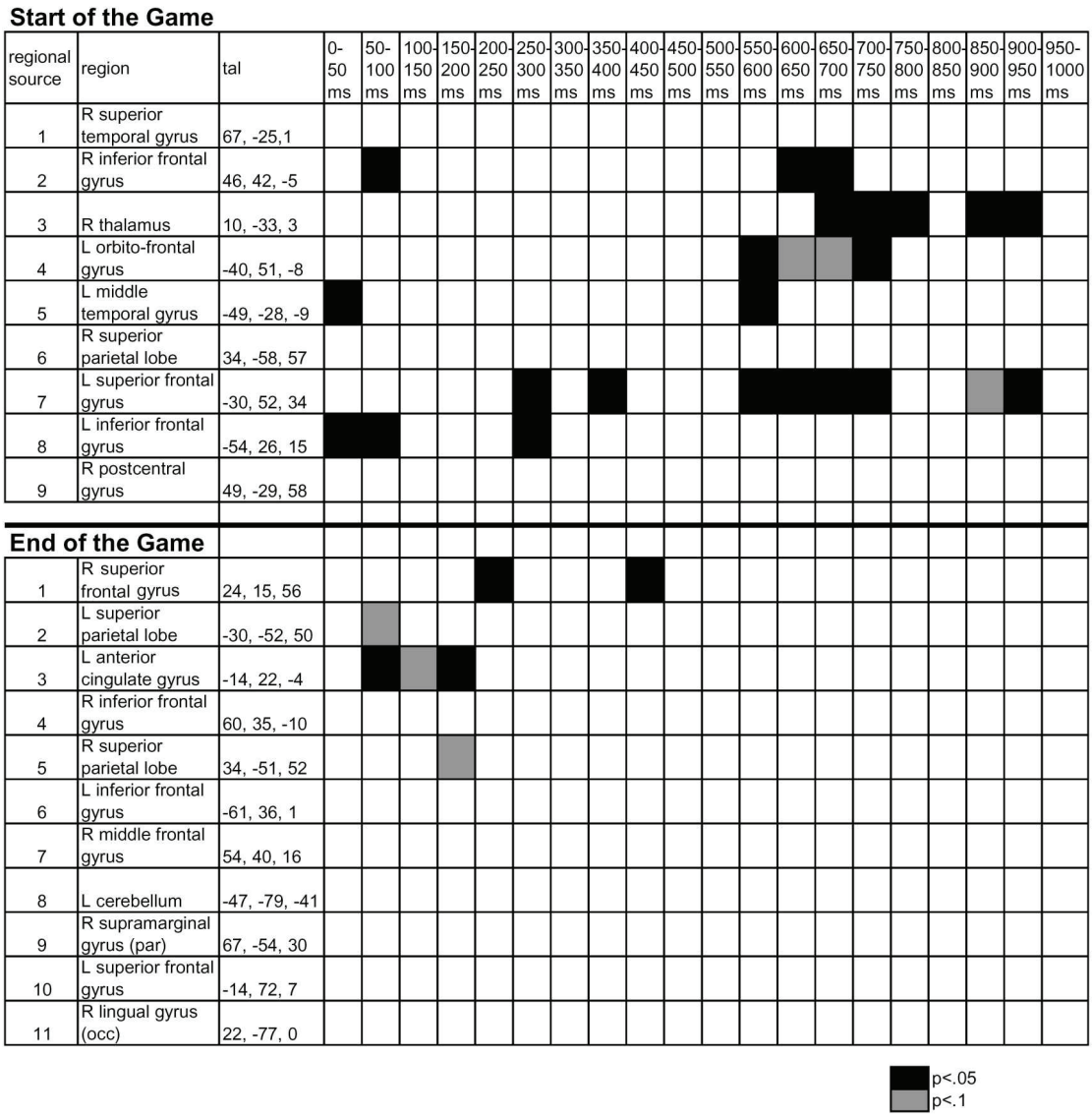

Figure 3.8 Significant post-hoc paired-sample t-tests indicating differences between OG and PG for the difference in RMS values between high-risk and low-risk (start of the game) and win and lose (end of the game) for 20 different 50 ms time windows between 0 and 1000 ms. RMS values were higher for PG compared to OG for all significant time windows; R=right; L=left.

3.3.4.2 Source analysis – Reward processing

For the phase of reward processing, during the end of the game, the applied source model (see Figure 3.9) consisted of right superior frontal and left superior parietal RS derived from the fMRI experiment.

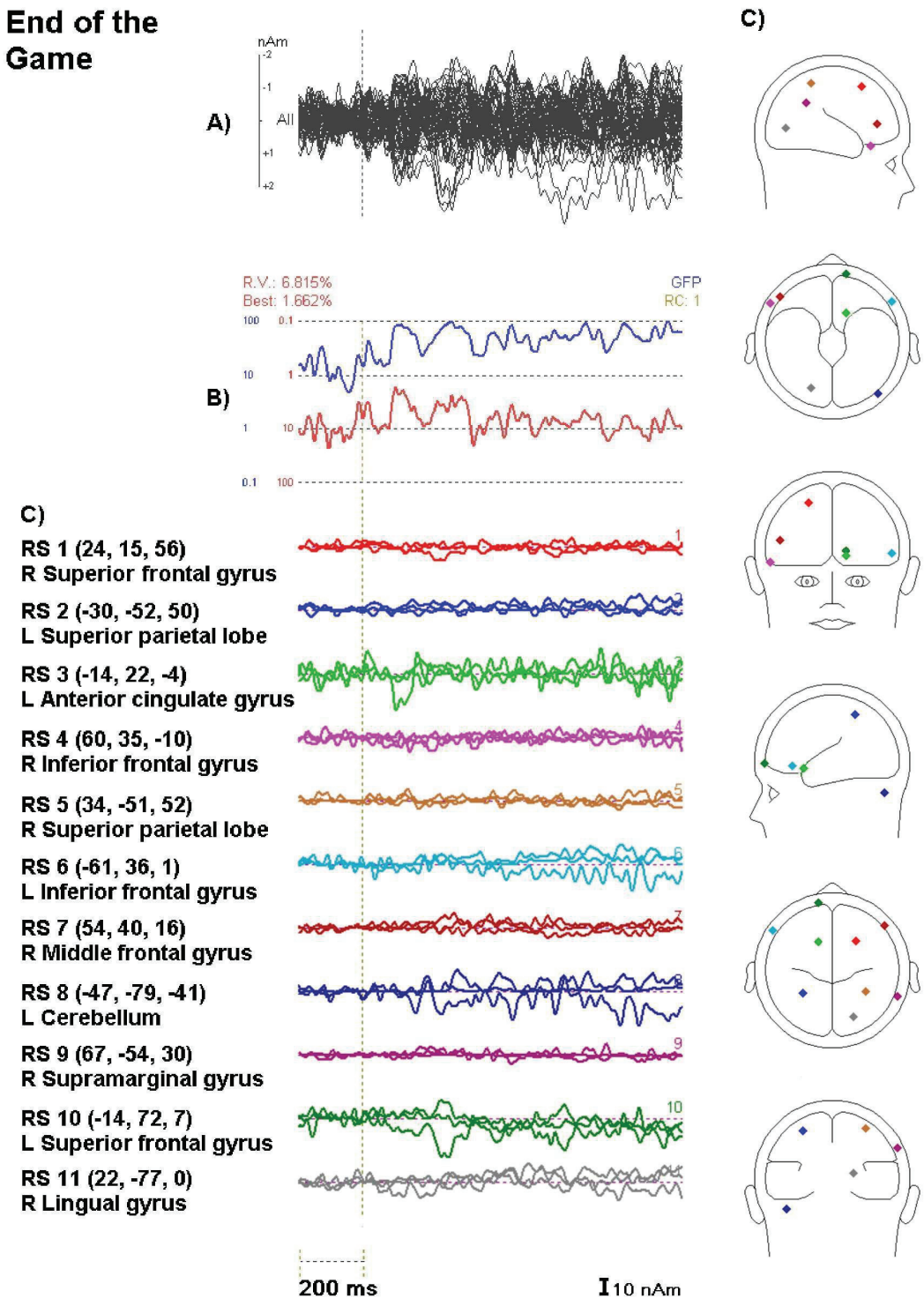

Figure 3.9 Source model for the end of the game: (A) Electrode overlay plot of the win vs. lose difference wave for PG minus OG (-200-1000 ms); (B) Global field power (GFP; blue curve) and residual variance [(RV) and best fit; red curve)]; (C) Regional sources (RS) with Talairach coordinates and scalp location (L=left; R=right). Regional sources 1 and 2 were seeded according corresponding fMRI peak activations – RS 3 to 11 were added by sequential fitting procedures.

Sequential fitting procedure for the 80-160 ms time window revealed additional left anterior cingulate, right inferior frontal, and right superior parietal sources. In addition, for the 200-1000 ms time window, sequential fitting resulted in left inferior frontal, right middle frontal, right cerebellar, right supramarginal, left superior frontal, and right occipital sources. In the appendix significant statistical main effects of group comparisons between OG and PG, significant GROUP x RS interactions (see appendix T 2), post-hoc statistics (see appendix T 4), and source waveform time-courses (see appendix A 18) are displayed in detail.

In the win vs. lose comparison, PG showed larger source moments than OG between 50 and 100 ms in left superior parietal regions (see Figure 3.8, lower part), and larger sustained source activity in left anterior cingulate gyrus (50-200 ms). Furthermore, PG showed larger source activity than OG in right superior parietal lobe (150-200 ms) and in right superior frontal gyrus (SFG; 200-250 ms and 400-450 ms).

3.4 Discussion – EEG study

In the following sections behavioral results, EEG results, and results of source analysis approach are discussed.

3.4.1 Behavioral data of the EEG study

Behavioral data derived from the EEG experiment showed a similar pattern as the behavioral data acquired in the fMRI study (see chapter 2.3.1). Decision behavior, reflected by the percentage of hit trials, in high-risk and low-risk situations during the start of the game did not differ between groups. This indicates, that PG did not behave more risky than OG during decision making in the present blackjack game. Furthermore, both groups did not differ in RT in low-risk and high-risk trials, which again reflects that PG and OG deal with different levels of perceived risk in a similar way on behavioral level. The fact that high-risk situations were accompanied by longer RT than low-risk trials in both groups suggests that both PG and OG might be slowed down by heightened conflict-related interference in high-risk situations (Yang et al., 2007). Another reason for the faster RT in low-risk compared to high-risk situations could be that low-risk trials facilitate decision making in both groups (Appelbaum et al., in press).

3.4.2 Discussion of the EEG data

The next sections outline the results of the electrophysiological data separately for the phases of risk assessment and reward processing. By using EEG, the aim was to look for electrophysiological correlates of risk assessment and reward processing in PG and OG during a quasi-realistic blackjack game.

According to the hypotheses raised prior to the experiment for the phase of risk assessment the results did not confirm early attentional or expert-related differences between PG and OG. However, the results corroborated group-specific modulations due to conflict processing and inhibitory control in the P3b time window. In addition, LPP modulation especially in PG might be related to enhancement of arousal in high-risk situations.

During reward processing assumed valence-related differences between PG and OG were confirmed due to group-specific ERP differences in an early time window, probably related to differential attentional processing in PG following winning vs. losing money.

Furthermore, later group-specific ERP modulation within the P3b time window suggests enhanced arousal, related to winning money exclusively in PG.

3.4.2.1 EEG data – Risk assessment

The following two chapters discuss EEG results with respect to risk assessment.

3.4.2.1.1 P3b time window

The higher mean amplitude in PG compared to OG in the high-risk vs. low-risk difference wave at parietal electrode positions (Pz, P4) was caused by amplitude differences in the high-risk relative to the low-risk condition between groups (see Figure 3.2). Whereas PG showed higher P3b amplitude in high-risk condition compared to low-risk condition, OG demonstrated the opposite pattern.

The higher amplitude at parietal electrode sites in the P3b time window for low-risk compared to high-risk trials in OG might reflect more intense processing of low-risk compared to high-risk decisions. One reason for this finding might be that low-risk situations signalize a save hit in OG, which, therefore, became more salient. Additionally, the enhanced P3b amplitude in OG in low-risk compared to high-risk situation might propose that low-risk decisions are accompanied by increased categorization processing in OG (Kok, 2001). In this sense, the focus of OG on safe low-risk situations with an heightened P3b amplitude might propose an elevated task relevance underlying categorization processing.

Furthermore, the enhanced P3b amplitude in PG in high-risk relative to low-risk decisions can be related to enhanced intensity processing (Donchin et al., 1986). High-risk decisions seem to be more attractive than low-risk decisions in PG and, therefore, are linked to an enhancement in intensity processing. According to Kok (2001) the event-categorization network is regulated by shared mechanisms of attention and working memory. Hence, high-risk situations, related to physiological arousal and euphoria (Legg England & Gotestam, 1991) might track enhanced attention in PG.

Another related concept explaining the higher P3b amplitude in high-risk situations in PG comes from Warren (1999), who related P412 enhancement to addiction cues in smokers. This might point to PG's attraction to high-risk decisions as these are perceived as more salient due to their incentive motivational function, because Warren (1999) argued that the P412 to smoking stimuli is related to activation of an automatic process, which fixates on

salient stimuli. Cue-reactivity in PG during high-risk decisions is in line with results of Gomez et al. (2008), who related increased P3b amplitude to enhanced context updating of working memory.

Left frontal and left temporal electrode positions (F7 and T7) showed lower mean amplitude in PG compared to OG in the high-risk vs. low-risk difference wave in the P3b time window. These P3a-like effects were mainly caused by amplitude differences between high- and low-risk decisions exclusively in PG. In terms of Davidson's (1992) approach/withdrawal theory the observed reduced left frontal positivity in PG high-risk compared to low-risk decision could reflect an indirect approach behavior for appetitive high-risk situations in PG due to reduced inhibition. This explanation is in accordance with a study by Polo et al. (2003), who related left frontal P3a enhancement to impaired involuntary attention in alcohol addicted persons after deviant tone presentation during a visual discrimination task. This is in agreement with the observed localization differences between PG and OG respectively to the amount of risk in the P3b time window to left middle frontal and orbitofrontal brain areas, since these regions are reported to be involved in salience assignment and motivation (Volkow et al., 2004). Polo et al. (2003) proposed, that disinhibition of the frontal executive system in alcoholic participants could have been responsible for encoding of novel auditory stimuli into working memory. In this sense, PG might be more distracted by low-risk compared to high-risk decisions because low-risk decisions might be perceived as boring and, therefore, disturb thrill-seeking gambling behavior. As a consequence, an extra amount of attention might be necessary to manage boring low-risk decisions in PG. This is in accordance with the dual-transmitter P300 hypothesis of Polich and Criado (2006), who proposed that P3a might be dopaminergic/frontal driven and, therefore, attention-related, whereas P3b is supposed to be NE/parietal driven and working memory-related.

To conclude, in PG tempting high-risk situations seem to be coupled with enhanced automatic engagement/approach, whereas low-risk decisions might need additional attention.

3.4.2.1.2 LPP-time window

Higher mean amplitude in PG compared to OG in the high-risk vs. low-risk difference wave at central electrode positions (Fz, Cz, Pz,) was caused by higher LPP amplitude in high-risk situations than low-risk situations only in PG (see Figure 3.2).

Dolcos & Cabeza (2002) reported increased positivity at fronto-central sites during recall of emotionally pleasant compared to unpleasant stimuli. In this sense, PG would perceive high-risk decisions as more pleasant, because engagement in thrill seeking behavior offers PG the opportunity to overcome lowered arousal levels resulting from abnormalities in mesolimbic brain structures (Goudriaan et al., 2004). This is in accordance with the interpretation that high-risk situations in the present experiment might be associated with lowered response conflict (Yang et al., 2007) in PG as a consequence of their disinhibition during high-risk situations. Moser et al. (2006) reported higher LPP following highly arousing unpleasant stimuli compared to neutral stimuli, which was intentionally modulated by task instructions. This pleads for LPP enhancement in emotionally arousing situations in general and more important, for a down-regulation of electrophysiological responses to motivational unimportant stimuli. In the present study, PG's intrinsic motivation during low-risk situations might have been weaker than in high-risk situations, which possibly led to a down-regulation of LPP amplitude in low-risk situations (Schupp et al., 2000). Furthermore, the heightened LPP in high-risk relative to low-risk decisions in PG might be related to enhanced interference processing during high-risk decisions. Liotti et al. (2000) related higher LPP during the incongruent Stroop condition to higher attentional processing, which might point to more extensive processing of high-risk situations in PG in the present study. Another possibility is that high-risk situations differ from low-risk situations with respect to gambling-related addiction memory in PG. High-risk situations with their thrilling character might function as addiction cues in PG and, therefore, remind PG of appetitive risky gambling situations, which in turn could interfere with risk assessment especially under high-risk conditions. In the present study source activity of risk-dependent differences between PG and OG in the LPP time window was localized to right superior frontal cortex, which Tanabe et al. (2007) associated with hypersensitivity to gambling cues. This is in accordance with studies (Franken et al., 2004; Wolfling et al., 2008), who reported LPP enhancement following drug cues in substance-dependent persons, suggesting cue-related craving in PG, triggered by high-risk situations. Craving might be directly coupled to action preparation, as the left middle temporal gyrus localization in the present experiment is associated with non-spatial response selection (Talati & Hirsch, 2005).

The present findings support the assumption that the augmented LPP during high-risk decisions in PG indicates heightened arousal accompanied by enhanced cue-reactivity with frontal and temporal generators.

3.4.2.2 EEG data – Reward processing

The following two chapters discuss EEG results with respect to reward processing.

3.4.2.2.1 Early time window

The higher N1 mean amplitude in PG compared to OG in the win vs. lose difference wave at fronto-central electrode positions (F3, Fz, Cz) was caused by stronger N1 amplitude in the win relative to the lose condition exclusively in PG (see Figure 3.4).

The observed differences can be related to heightened attentional processing of win compared to lose situations in PG (Hillyard, 1993). OG showed no N1 differences between positive and negative reward in early time windows and, therefore, might not differ on attentional levels between win and lose situations, and hence dealt with those situations in a similar way. This is in line with Fehr et al. (2006), who demonstrated early P1/N1 enhancement of smoking-related words in smokers while performing a nicotine Stroop task. The authors interpreted elicited P1/N1 amplitude in smokers in terms of enhanced attention, related to addiction memory and heightened sensitivity for drug-cues. These early effects in the present experiment were localized to orbitofrontal and middle frontal cortex, which is in accordance with Crockford et al. (2005), who reported greater orbitofrontal and DLPFC activity in PG compared to controls during visual presentations of gambling-related cues. The authors concluded that PG displayed priority in recognizing gambling cues, because they were salient for attention, expectancy of reward, and behavior related to achieving rewards. The additionally found localization in postcentral gyrus could be directly related to attentional processes and motivational relevance (Lloyd et al., 2006). With respect to the present thesis, PG might, therefore, have expressed a general enhancement of arousal, allowing them to differentiate win from lose situations in this early time window. Another explanation for this rapid content discrimination by ERPs comes from Anokhin et al. (2006) who reported early ERP differences elicited by erotic contents compared to emotionally positive, negative, and neutral pictures. The results were interpreted in a way that biologically crucial stimuli have to be processed faster than other stimuli. The observed difference between win and lose situations in the present dissertation might be of essential character for PG, because winning money is a relevant requirement, enabling them to place the next bet to continue with gambling. Ehlers et al. (2006) reported heightened attentional level reflected by N1 enhancement to affective stimuli in

participants with PTSD, which was discussed in the way that disorders-related cues increase attention, which is in line with the here detected enhanced processing of win trials in PG. Winning money, as a core component of gambling might be coupled with stronger attentional processing than lose trials because in "high-risk gamblers" winning money strengthened the desire to persist in gambling in comparison to losing money (Young et al., 2008).

To conclude, early valence-related differences during reward processing in PG might point to enhanced attentional levels in win situations due to their probable function as addiction relevant cues.

3.4.2.2.2 Late time window

Higher mean amplitude in PG compared to OG in the win vs. lose difference wave at right central electrode position (C4) was caused by higher amplitude (between 390 and 440 ms) in win situations than lose situations in PG, whereas OG showed the opposite pattern (see Figure 3.4).

This result can be interpreted as strengthened cue-reactivity (Warren & McDonough, 1999), in the sense that PG might be more aroused in win situations, which seem to be more salient than lose situations. The fact that OG showed higher positivity in lose situations might reflect stronger arousal. OG seem to be more emotionally affected during losing compared to winning money, which is probably related to the fact that they played for real money. These results are in line with Rozenkrants & Polich (2008), who reported larger P3 amplitudes in high-arousing compared to low-arousing faces irrespective of the valence of the faces. The authors interpreted their results in a way that P3 enhancement in high-arousing situations might be related to goal-directed engagement of attention and subsequent memory processing. With respect to the results of the present thesis, it could be argued that both PG and OG might have expressed goal-directed attention. Consequently, in PG high arousal levels might be coupled to win situations, whereas in OG high arousal might be associated with lose situations. Source localization in the present study revealed right superior parietal regions, which have been reported to be involved in numerical magnitude processing (Dehaene et al., 2004; Pesenti et al., 2000). This might reflect group-specific differences during the integration of wins vs. losses in the current asset of each player. The found left superior frontal sources, observed previously after presenting gambling or addiction cues (McClernon et al., 2009; Tanabe et al., 2007), serve as

evidence for valence-related differentiation in arousal between PG and OG as a reaction to appetitive win situations especially in PG.

Increased negativity in PG compared to OG in the win vs. lose difference wave at left parietal electrode position (P7) was caused by lower amplitude (between 390 and 440 ms) in win situations than lose situations in PG, whereas OG showed the opposite pattern (Figure 3.4). The generally enhanced amplitude over P7 electrode position in PG compared to OG could reflect long-term perceptual expertise (Scott et al., 2008), as PG might be more trained to process information regarding winning or losing money. In addition, left parietal P7 electrode amplitude increase in PG might be related to strengthened attention or context updating in working memory (Gomez et al., 2008) during win situations in PG, whereas OG indicated heightened attention in lose situations. Another explanation with respect to the left lateralized activity in the 390 – 440 ms time window concerns the fact that crucial information about winning or losing the game was presented on the middle to the right side on the screen. The important cards, indicating a win or a loss of money were presented successively at the middle (card 3) to the right side (eventually card 4 and card 5 of the dealer) of the screen, therefore, context updating always ended at these positions. This could have shifted local attention to the right side of the screen and as a consequence P3b effect due to attentional context updating, normally observed centrally on Pz, was displayed at left parieto-occipital electrode position P7.

In summary, group-specific differences in reward processing in later time windows might point to cue-reactivity in PG, in the sense that win situations might function as specific cues, permitting further gambling activity.

3.4.2.3 Summary and conclusion of the ERP data - Limitations of the study

Comparing PG to OG within a quasi-realistic blackjack game, ERP modulations in three time windows could be observed. Early time windows revealed group-specific differences during reward processing, which might reflect enhanced attentional processing during win situations in PG. Source localization of this effect to orbitofrontal and middle frontal cortex supports a preferred processing of salient gambling-related cues in PG.

In the P3b time window high-risk as well as win situations lead to intensified processing/context updating in PG. High-risk situations seem to be more tempting in PG than OG where heightened task relevance might be coupled to diminished inhibitory

control in PG. In addition, appetitive win situations are expected to trigger further gambling behavior especially in PG.

Late time windows indicated enhanced slow wave ERP in high-risk situations exclusively in PG, which might be related to heightened arousal or cue-related craving.

The limitations of the present study are similar to that reported for experiment 1 (see last paragraph of chapter 2.4.4). In experiment 2 only eight participants of the PG group fulfilled the criteria of PGG on DSM IV - four had a diagnosis of problem gambling. Nevertheless, all participants in the PG group fulfilled the SOGS and KFG criteria for PGG. Again, the OG group differed from "normal control participants" in other studies regarding gambling experience.

3.4.3 Differences in source activities between PG and OG

Up to now, this is the first study investigating risk assessment and reward processing in PGG with a combined EEG and fMRI approach. By combining high temporal resolution of the EEG method with good spatial resolution of fMRI it was possible to identify successive active brain regions in PG and OG during the two phases of the blackjack game. The advantage of applying fMRI constrained source analysis is grounded in a combination of temporal and spatial dynamics while including prior information of significant fMRI sources to improve the validity of the model (Hopfinger et al., 2005; Scherg & Berg, 1991). Two discrete models were created, one for the start of the game where participants had to decide to draw or not to draw an additionally card under different levels of risk. The first model consisted of three significant brain regions of the fMRI study (see Figure 2.2) completed with six additional seeded sources. The second model was created for the end of the blackjack game, where participants perceived financial wins or losses. This model was composed of two sources from the fMRI study (see Figure 2.3) complemented with nine additional seeded sources.

In the following sections, differences between PG and OG in the high-risk vs. low-risk (risk assessment) and win vs. lose comparison (reward processing) are discussed.

3.4.3.1 Sequence of regional source activities during risk assessment

The fMRI constrained RS model during risk assessment revealed that PG demonstrated larger source strength than OG in the high-risk vs. low-risk comparison in left middle temporal (0-50 ms), right inferior frontal (50-100 ms), and left inferior frontal cortex

(0-100 ms), followed by differences in left inferior (250-300 ms), left superior frontal (250-300 and 350-400 ms), middle temporal (550-600 ms), left orbitofrontal and superior frontal (550-750 ms), and right inferior frontal sources (600-700 ms). In addition, PG showed increased source strength compared to OG in the thalamus (in the 650-800 ms and 850-950 ms time window) and in the left superior frontal cortex (850-950 ms).

3.4.3.1.1 Early group-specific modulations

Early left (0-100 ms) and right (50-100 ms) inferior frontal group differences in high-risk compared to low-risk situations might be related to early attentional processes. PG seem to differentiate attentional levels in high-risk from low-risk situations in another way than OG, which might be related to attentional modulation of IFG during cue updating exclusively in PG (Pessoa et al., 2009). Furthermore, Garavan et al. (2000) reported similar bilateral IFG activity in answer to the experience of cocaine cues vs. naturally arousing cues in cocaine users. The authors concluded that drug cue processing in cocaine users might be based on learning and activates pathways, which are active in healthy persons during evocative stimulus processing. With respect to the present thesis, this would mean that tempting high-risk situations function as an arousing gambling cue in PG, reflected by early automatic processing.

Another explanation for the found group-specific IFG differences during risk assessment might be, that PG and OG show differences in early selection processing. Thompson-Schill et al. (1997) reported the important role of the left inferior PFC in the selection of semantic knowledge among competitive options from semantic memory. In this sense PG might be focused attentionally on appetitive high-risk situations, which could in turn be coupled to automatic selection. PG seem to be driven by their addiction memory, which automatized selection processing of gambling-related cues. In the present thesis left IFG activity differences between PG and OG were observed within the first 50 ms after stimulus presentation, which might reflect very early approach behavior in PG to attractive high-risk situations (Davidson, 1992).

Kaufmann et al. (2003) linked diminished left inferior frontal activation within a go/no-go task paradigm directly to unsuccessful inhibitions in cocaine users. The authors stated that addicted people have problems with the volitional control of their behavior. As a consequence, stimuli of the environment, such as drug cues and habits, control a great part of their behavior. With respect to the present experiment, a generally reduced inhibitory

activity in PG might result in a heightened susceptibility to gambling-related cues, such as high-risk situations. Consequently, IFG might be involved in the preferential processing of gambling-related cues in PG. Support for an important role of the bilateral IFG in drug craving comes from Xiao et al. (2006), who tested water and drug deprived heroine addicted persons while presenting drug-related, water-related, and neutral cues. Drug-related cues elicited bilateral IFG, while water cues activated ACC. The authors linked ACC activity to be important in the formation of thirst, whereas IFG was concluded to play an important role in drug craving. Alternatively, Xiao et al. (2006) speculated that IFG might become active since participants knew that the drug was unavailable during the experiment, hence craving had to be suppressed through IFG activity. Concerning the early IFG activity in the present thesis, inhibition could be ruled out, because it would function as a reaction to an early attentional or perceptual process, preceding inhibition.

Another argument for the early modulation in inferior frontal regions comes from a combined fMRI and EEG study of Qin & Han (2009), who reported increased left IFG activity to the identification of personal risks measured by fMRI, which was thought to be related to induced early positive ERP deflections over frontal electrode positions. Interestingly, the authors concluded that an early frontal detection process manages risk identification and that personal variables might modulate this process. This is in accordance with the results in the present thesis in the sense that PG with their gambling history might accomplish early identification of high-risk and low-risk situations.

Matsunaga et al. (2009) reported IFG activity during the experience and detection of positive emotions. The authors discussed the IFG as well as the STG and thalamus as being part of a sensory system that detects emotional stimuli. This fits to the result of the fMRI study (see chapter 2.3.2), where an interaction analysis showed larger contrasts in PG compared to OG for high-risk vs. low-risk conditions in right superior temporal, right inferior frontal, and right thalamic brain regions. The reported sensory character of IFG reflects the early group-specific modulation of brain activity in the present experiment.

Early (0-50 ms) left middle temporal group differences in high-risk compared to low-risk situations might be associated with enhanced visuospatial attention in PG during high-risk processing. This is in accordance with Chen et al. (2009), who linked right middle temporal gyrus (MTG) activation in a fMRI conjunction analysis between narrowly and widely focused attention to the control of spatial attention. Furthermore, PG might identify high-risk situations with higher priority than low-risk situations, as high-risk situations might be more familiar to them (Vingerhoets, 2008). PG with its disorder intrinsic risk-

seeking behavior might be more habituated to high-risk situations and, therefore, were more familiar to high-risk situations compared to low-risk situations. Furthermore, left MTG was reported to play an important role in semantic memory retrieval during meaningful gesture identification (Villarreal et al., 2008) and retrieving of conceptual knowledge (Tranel et al., 1997). Regarding the results of the present thesis, PG might identify tempting high-risk situations very fast as they might be considered more meaningful than low-risk situations. High-risk assessment/decision making seems to function as a basic concept in PGG, which can be retrieved very fast from addiction memory. The fast processing of gambling-related stimuli might have been feasible through immediate perception of the high-risk situation as an entity – not as loose local elements of single cards. Support for this idea comes from Seymour et al. (2008), who reported left MTG activity during gestalt grouping. Observing goals vs. means of an action activated left middle temporal gyrus (Hesse et al., 2009), which points to a goal or context sensitivity of the MTG. In the present experiment, the goal of PG might be to engage in attracting high-risk situations, accompanied by enhanced attention towards this specific context. The differential processing of high-risk compared to low-risk situation in the left MTG of PG might be related to automatic priming via attentional mechanisms. Copland et al. (in press) reported enhanced MTG activity during lexical decision priming of dominant meaning (e.g. bank-money) but not for subordinate meaning (e.g. fence-sword) under Levodopa medication in healthy participants. The authors linked their findings to dopaminergic strengthening of semantic networks, which are important in semantic priming. Furthermore, the study supported the evidence of dopaminergic receptors in the temporal lobe and their important role in automatic semantic priming. An important conclusion of Copland et al. (in press) was that enhanced dopaminergic transmission strengthened the selection of competing representations by enhancement of relevant and reduction of irrelevant representations. Within PG it could be the case that learned gambling cues trigger the dopaminergic system, which leads to heightened stimulus salience (Schultz, 2002) and approach behavior (Davidson, 1992), especially in high-risk situations.

To conclude, early group-specific modulations within 100 ms after the presentation of high-risk vs. low-risk situations were reflected by bilateral inferior frontal and left middle temporal differences. Regarding the literature, it might be the case that these differences represented heightened attention to gambling cues coupled with approach behavior to appetitive high-risk situations, exclusively in PG.

3.4.3.1.2 Group-specific modulations between 250-400 ms

Left inferior frontal group differences in high-risk compared to low-risk situations in the 250-300 ms time window might be connected to evaluative stimulus processing during risk assessment. Evidence for an important role of the left IFG during risk assessment comes from Paulus et al. (2003). They observed left IFG activity in methamphetamine-dependent persons when stimulus uncertainty was highest, whereas healthy control participants demonstrated success-related activation patterns. The authors concluded that methamphetamine-dependent persons are more stimulus driven. PG share core components with stimulant-dependent patients (Glicksohn et al., 2007) in the sense that both groups' behavior is dominated by habit-based learning, with stimuli intensely acting on response selection regardless of related results (Robbins & Everitt, 1999). For results of the present study this could mean that enhanced IFG activity in PG during high-risk decisions reflects a stimulus driven approach behavior for maximally uncertain situations.

Furthermore, left IFG activity was reported to be involved in risk assessment (Vorhold et al., 2007) when responses of a risk rating task were compared to those of a letter detection task. In the present study, the heightened left IFG activity in PG might point to differences in rating high-risk compared to low-risk situations. Due to the fact that the results of the present source analysis are derived from the group (PG vs. OG) x risk (high-risk vs. low-risk) interaction it is only possible to compare the neuronal responses between PG and OG on differences between levels of risk and not on absolute risk level (high-risk and low-risk separately). Because of that, it could have been the case that PG demonstrated augmented risk perception in high-risk situations or diminished risk perception during low-risk situations. Zysset et al. (2002) reported left IFG activity during evaluative judgments. The authors concluded that the left IFG plays an important role during information selection among other competing options. In PG high-risk situations seemed to be linked to strengthened evaluation than low-risk situations. It might be the case that high-risk situations trigger gambling memory in PG, with these tempting situations leading to enhanced information processing. An alternative interpretation for the results would be that boring low-risk situations were linked to weakened evaluation in PG.

The found left superior frontal group-specific modulations between high-risk and low-risk assessment in the 250-400 ms time window might be affiliated with early arithmetic operations. Fehr et al. (2007a) reported similar left superior frontal activations during subtraction of digits. In the present dissertation, PG might show enhanced arithmetic processing during attractive high-risk situations, while calculating the points of their cards,

which could alternatively be linked to support the management of consecutive operations in working memory (Dehaene et al., 2004). Tucker et al. (2004) showed that heightened resting perfusion (measured by SPECT; Single Photon Emission Computed Tomography) within cocaine-dependent patients' left superior frontal cortex was associated with worse performance on the IGT, which they related to impaired cognitive factors. Consequently, left superior frontal cortex seems to be play an important role during affected risk assessment in addicted persons although behavioral results in the present study (see chapter 3.3.1) do not point to group differences in risk taking.

Mc Clernon et al. (2009) demonstrated greater left superior frontal activity in 24 hours abstinent smokers compared to satieted smokers while viewing smoking cues vs. control cues which they related to enhanced salience of addiction cues. Consequently, the found group differences in the SFG during the start of the game might be connected to strengthened salience of high-risk relative to low-risk stimuli exclusively in PG.

Another evidence for the important role of superior frontal cortex in the processing of addiction-related cues comes from Yang et al. (2009). The authors compared heroin addicted vs. healthy persons and observed lowered signal in superior frontal cortex after viewing neutral cues, and enhanced signal for heroin cues. These results are again in accordance with the heightened activity in left superior frontal cortex during high-risk compared to low-risk situations in PG in the present thesis, which might be related to cue-reactivity or hypersensitivity to gambling cues (Tanabe et al., 2007).

In summary, group-specific differences in high-risk compared to low-risk assessment in the 250-400 ms time window in the IFG and SFG might suggest early evaluative stimulus processing, working memory involvement, or prolonged cue-reactivity in PG.

3.4.3.1.3 Late group-specific modulations

Group-specific effects between high-risk and low-risk assessment in the late time windows were found in superior frontal, inferior frontal, orbitofrontal, middle temporal, and thalamic regions.

Left middle temporal differences in the 550-600 ms time window might be associated with non-spatial response selection (Schumacher et al., 2003; Talati & Hirsch, 2005). It might be the case that PG show a higher level of response selection activity than OG during high-risk compared to low-risk situations. An explanation is that strengthened early attentional processing during high-risk situations in PG could have modulated response selection

process later in time. The fact that left MTG was also reported to be active during action word processing (Davis et al., 2004; Hauk et al., 2008) and during the naming of action words (Martin et al., 1996) create evidence for an involvement of this region in goal-directed processing. Consequently, left MTG might be an important part of a brain network, grounding language and concepts in perception-action systems (Hauk et al., 2008). This is in line with Sass et al. (2009) who highlightened MTG to be involved in semantic integration over different modalities and in the automatic semantic processing of directly related words or sounds. The MTG seems to be important in object or concept representation, functioning in a goal-directed manner, and influencing both perception and response selection. In PG habit-based learned gambling concepts might influence both perception of addiction cues as well as the reactive processing of them, where the MTG seems to play a crucial role in both processes.

Right IFG activation differences between groups at 600-700 ms might be related to competing perceptual interpretation of the high-risk compared to the low-risk assessment exclusively in PG (Sterzer & Kleinschmidt, 2007). In PG low-risk situations seem to be easy to handle, whereas appetitive high-risk situations might be higher in uncertainty or conflict in the sense that a gambling expert wants to make a good decision there. OG might not make this difference between high- and low-risk assessments. A related argument might be that the higher right IFG activity during high-risk vs. low-risk situations in PG reflects heightened response inhibition (Aron et al., 2004). PG seem to be more aroused in high-risk compared to low-risk situations within 100 ms after stimulus presentation (see upper part of Figure 3.8). Consequently, in a later time window (600-700 ms) PG might inhibit themselves in high-risk situations more than in low-risk situation to make a reasonable decision. Vanderberghe et al. (1999) reported right IFG activity when a learned stimulus-response association had to be retrieved and attuned to a new context. In PG every high-risk situation might create a new context, where the learned gambling behavior had to be adapted to. Low-risk situations with its probable boring character might be played with a routine behavior and did not need context adaptation in PG. Another possibility would be that this activity reflected again cue-induced signal increase (Crockford et al., 2005) or increased attention (Hampshire et al., 2009) as a reaction to arousing high-risk situations.

The found group-specific modulations in left SFG between high-risk and low-risk assessment in late time windows might be again related to arithmetic operations (Fehr et al., 2007a) or hypersensitivity to gambling cues (Tanabe et al., 2007). Furthermore, the

results could point to task switching processes (Cutini et al., 2008). The cognitive tasks underlying high-risk and low-risk assessment might be different in PG compared to OG. This would implicate that principles preparing a decision to draw or not to draw an additional card in a high-risk situation vs. a low-risk situation seem to differ between groups. It could be that blackjack strategies are generally more dominant in PG, implicating switching between high-risk and low-risk decision strategies on a conceptual level. OG might play less strategic and, therefore, switch between high-risk and low-risk decisions on a more perceptual level. Woo & Lee (2007) reported left SFG activity during response selection which correlated positively with the number of alternative responses. The authors related their effects to higher load of response selection. Additionally, left SFG is involved in the monitoring and manipulation of working memory, which is overruled by increased task demand (du Boisgueheneuc et al., 2006). This fits to the idea that PG might express a strengthened demand to determine or to control the outcome of uncertain events (Goodie, 2005), especially during high-risk assessment.

Left SFG was reported to be active during up regulating of emotion (Ochsner et al., 2004), when participants had to increase their negative emotions in response to aversive images. The authors related their results to the retrieval of emotion knowledge which was incorporated in the perception of the stimulus material. This could mean that PG automatically intensify their emotional involvement in attracting high-risk situations through addiction memory retrieval.

The right thalamic differences at 650-950 ms (with exception of 800-850 ms) between PG and OG in high-risk vs. low-risk situations might reflect cue-induced craving activity (Volkow et al., 1997; Wang et al., 2007). Furthermore, the thalamus was reported to play a key role in emotional experience and expression (Nummenmaa et al., 2008), as well as motivation and drive (Schmahmann, 2003; Sewards & Sewards, 2003) (see also chapter 2.4.1). Elliott et al. (1999) found right dorsomedial thalamus activity when guessing was compared to reporting the color or suit of a card. The authors related their results to working memory processes (Mitchell et al., 2008) or high level executive functions. Due to the broad involvement of the thalamus in different processes it might be the case that this region function as a mediator, enhancing cognitive functions as a reaction to high-risk gambling cues in PG.

Left OFG was differently active in PG vs. OG in high-risk compared to low-risk situations in the 550–750 ms time window. Support for the important role of the OFG in cue-induced urge for gaming comes from Ko et al. (2009) who compared online gaming addicted

persons (World of Warcraft game) to healthy participants while viewing gaming vs. mosaic pictures in a fMRI study. Goldstein & Volkow (2002) stated that one function of the OFG is to attribute salience to a specific stimuli, which is important for the evaluation of drug-related context in the future. For the results of the present dissertation exclusively PG might attribute higher salience to high-risk than to low-risk situations. In addition OFG is thought to play an important role during risk assessment where the medial OFG seems to be involved in the monitoring, learning and memory of the reward value of reinforcers, while the lateral OFG might be crucial in the assessment of punishers, possibly causing behavioral alterations (Kringelbach, 2005; Kringelbach & Rolls, 2004). In the present thesis the observed group-specific differences were located in the lateral part of the OFG. Therefore, it can be concluded that a probable financial loss during high-risk compared to low-risk assessment is evaluated differently in PG, which fits to the lateral OFG involvement in uncertainty processing (Tobler et al., 2007) with NE as a possible underlying neurochemical substrate (Doya, 2008). High-risk trials might be perceived as more uncertain than low-risk trials only in PG, whereas OG might demonstrate a generally elevated level of uncertainty irrespectively of the perceived risk. Furthermore, the reported anterior OFG activation in the present dissertation might be related to subjective pleasantness (Kringelbach & Rolls, 2004) perceived in PG during high-risk assessment.

The OFG plays also a crucial role in processing emotional or somatic signals during decision making (Bechara, 2004), such as impulse control or the inhibition of undesirable memory or thoughts (Bechara, 2005). In the present dissertation the higher OFG activity in PG than in OG during high-risk assessment might be related to enhanced somatic signal processing of gambling cues, especially during appetitive high-risk situations.

Altogether, group differences in the late time window between high-risk and low-risk assessment activated a frontal, temporal, thalamic network, reported to be involved in subjective task demand updating, impulse control and emotional perception-action coupling.

3.4.3.1.4 Summary of regional source activities during risk assessment

In summary, group differences in the high-risk vs. low-risk comparison have been observed in early, middle, and late time windows. High-risk assessment in PG might be characterized by early enhanced cue-induced attentional processing at frontal and temporal locations, followed by heightened evaluative stimulus processing and mental arithmetic

activity at frontal regions, continued with affective and arousal guided goal-directed processes like updating task demands and perception-action coupling in late time windows in a frontal, temporal, thalamic network.

3.4.3.2 Sequence of regional source activities during reward processing

During reward processing as derived from contrasting winning vs. losing situations, PG compared to OG demonstrated enhanced fronto-central N1 amplitude, followed by centro-parietal differences in the P3b time window. Source power during reward processing yielded larger source strength of PG than OG in left superior parietal regions (50-100 ms) and more sustained activity in left anterior cingulate gyrus (50-200 ms). Further transiently enhanced source power was revealed for right superior parietal lobe (150-200 ms), followed by right middle frontal gyrus (200-250 and 400-450 ms).

3.4.3.2.1 Early bilateral parietal win-lose differences between groups

Left superior parietal differences between groups in the win vs. lose comparison at (50-100 ms) might be related to number processing (Dehaene, 2003) and representation of quantity (Dehaene et al., 2004). It could be the case that PG process the win of money more intensely than a loss of money, since winning has been shown to increase the desire to continue gambling in problem gamblers (Young et al., 2008). The authors related their results to priming effects of win trials on a future gambling episode. This would implicate that PG perceive win situations as motivational cues facilitating processes such as updating their running total or preparing further gambling behavior. Another possibility is that losing money might have been ignored by PG and, therefore, general processing in lose trials was attenuated. In addition, Yalachkov et al. (2009) found left superior parietal, bilateral premotor, and cerebellar activity in smokers while viewing smoking-related cues. The authors reported that in these regions addiction-related representations of actions are probably stored. Therefore, the observed group-specific superior parietal differences between winning and losing money might be linked to enhanced gambling cue processing in PG. The fact that the left superior parietal gyrus was reported to be important in planning and selection of general tool use principles (Goldenberg & Spatt, 2009; Kroliczak & Frey, in press) as well as the preparation of abstract stimulus-response associations (Cavina-Pratesi et al., 2006), creates further evidence for the probable goal-directed character of win situations in PGG.

Bilateral superior parietal lobe (SPL) activity was reported to correlate positively with enhanced demand of visuospatial attention (Vannini et al., 2004). Consequently, only PG might have demonstrated heightened visuospatial attention to high demanding win situations. Support for this idea comes from Chiu & Yantis (2009), who related medial superior parietal activity to be involved in the shift of spatial attention and in the switch between rules of categorization. It was concluded that the reported brain region is crucial for an effective endogenous preparation for future tasks (Jankowski et al., 2009). The observed superior parietal activity in PG could also reflect augmented attentional processing due to addiction memory involvement only in win trials, since this region was reported to be involved in orienting attention to both internal (mental representations) and external (perception) events (Lepsien & Nobre, 2006; Nobre et al., 2004). Ciaramelli et al. (2008) linked SPL to environmental top down aspects of attention and inferior parietal lobe (IPL) to working memory-related bottom up processes of attention. As the left SPL RS in the present dissertation was derived from fMRI activation of both SPL and IPL it might be the case that voluntary and automatic attention have influenced the strengthened processing of win situations in PG.

Summarizing, early bilateral SPL/IPL differences between PG and OG in win vs. lose trials might point to enhanced attention, number processing, and action preparation during win situations exclusively in PG.

3.4.3.2.2 Early left ACC group differences in the win vs. lose comparison

Higher activation in left ACC in PG than in OG during the win vs. lose comparison might be associated with emotional processing. Bush et al. (2000) discussed a probable functional differentiation within the ACC, where the dorsal ACC (projecting to DLPFC and motor cortex) represents the cognitive division and the rostral-ventral ACC (with projections to OFC, striatum, hypothalamus and brainstem) the affective division. The ACC source of the present dissertation was located in the rostral-ventral part of the ACC and, therefore, emotion-related, which can be interpreted with higher affective involvement of PG during winning relative to losing money. This is in line with Salloum et al. (2007), who reported lower rostral ACC activity during perception of negative facial emotions in alcohol patients compared to healthy controls, whereas both groups did not differ in rostral ACC activity during the perception of positive facial emotions. The authors discussed the results with respect to the risk or sensation seeking personality of alcoholic patients,

demonstrating problems in avoiding cues that signalize danger. Since PGG as a drug-free addiction (Potenza et al., 2003b) and an obsessive-compulsive spectrum disorder (Blanco et al., 2001) shares similarities with substance use disorders (Potenza, 2008), PG might also have demonstrated attenuated rostral ACC performance during the processing of lose trials. This might create evidence for a limited detection of dreadful risks in the environment (Qin & Han, 2009) by PG.

In addition, ACC was reported to be involved during pleasure processing (McLean et al., 2009), sexual arousal (Karama et al., 2002), as well as during winning vs. losing money (Rogers et al., 2004). These results strengthen the role of the ACC in the processing of intense emotions. Consequently, in the experiment of the present thesis it seems that PG had made a clear difference between the intensity of affective processing of win vs. lose situations in blackjack. Furthermore, McClernon (2009) reported positive correlation between pre-scan craving and smoking cue activation rostral ACC, dorsomedial PFC, SFG, and supplement motor area in smokers, which they interpreted as enhanced salience of conditioned cues. The observed heightened ACC activity in the present experiment demonstrates that especially win trials might function as high salient gambling cues in PG.

As the source analysis in the present study was based on differences between win and lose situations there are three possible interpretations for the found ACC activity. First, it could have been that PG demonstrated attenuated emotional processing of lose trials relative to normal processed win trials. Second, PG might have shown normal affective processing of lose trials relative to enhanced processing of win trials. Third, PG might have displayed both heightened emotional processing of win and attenuated affective processing of lose trials. The first and the second possibility point to valence-specific enhancement/attenuation in emotional processing of PG, whereas the third alternative reflects an involvement of both valences. Reviewed results of Kalivas & Volkow (2005) are in agreement with the third option as they reported ACC and OFC hypoactivity in addicted persons to biological relevant cues (Garavan et al., 2000) as well as hyperactivity in the same regions to addiction relevant cues (Volkow et al., 1999), which the authors claimed to be responsible for compulsive drug intake. This line of argumentation can be easily transferred to the present results, where PG showed enhanced ACC activity in win situations, which in turn might be responsible for further compulsive gambling behavior.

Dalgleish (2004) proposed an important role of the ventral ACC in monitoring conflict between the functional state of the organism and any new information that has potential emotional or motivational consequences. He argued that the ACC projects conflict-related

information to the PFC where the decision between different response alternatives takes place. The motivation-related ACC enhancement to control other brain areas to maximize utility (Pessoa, 2009) might be different in PG compared to OG in the sense that PG demonstrate a motivational tendency for appetitive win situations. This "maximization of utility principle" in healthy persons (maximization of reward and minimization of punishment) might be shifted to excessive maximizing of reward coupled by an incapability to minimize punishment in PG.

Altogether, higher ACC activity in PG than in OG in the win vs. lose comparison might point to differences in affective stimulus processing between groups. Especially PG seem to demonstrate heightened emotional processing in win situations coupled to attenuated ACC response during lose trials, possibly leading to compulsive gambling behavior in PG. One underlying reason might be that PG indicate problems in conflict monitoring between inner states of the organism and cues of the environment.

3.4.3.2.3 Right superior frontal differences during reward processing

Right superior frontal differences between OG and PG in the win vs. lose comparison (at 200-250 and 400-450 ms) might be related to motor preparation (Toni et al., 2002) and imagery (Rizzolatti & Craighero, 2004). Furthermore, superior frontal/middle frontal activations were reported to be enhanced during viewing addiction-related cues in heroin-dependent persons (Yang et al., 2009). The authors discussed a network consisting of SFC, DLPFC, and OFC, which seems to function as an integrator against distractions until the task to attain the goal and to consume the drug is accomplished. This findings might implicate an attenuated processing of drug-unrelated stimuli combined with an enhanced processing of drug-related stimuli in PG, which is similar to the argumentation for the processing of biological vs. addiction relevant cues in the previous section for the ACC and OFC (Kalivas & Volkow, 2005).

Yalachkow et al. (2009) linked bilateral premotor activity to action execution, being important for the selection of appropriate sequences of motor commands based on cues. In the experiment of the present thesis the observed superior frontal differences between win and lose situations in PG might demonstrate enhanced preparatory activity during win trials. Consequently, winning money seems to trigger the engagement of PG in further gambling behavior which makes sense because obtaining money could function as a precondition to be able to continue gambling at all. This is in accordance with Smolka et

al. (2006) who speculated about the involvement of the premotor cortex in addictive behavior due to habitually over-learned actions. PGG could, therefore, be maintained as this once learned addictive behavior in turn might facilitate addiction-related action selection via shifting action goals from biological relevant to addiction relevant.

Pineda & Oberman (2006) demonstrated enhancement in the mu frequency band (8–13 Hz) on premotor cortex electrodes while viewing addiction-related movement cues in smokers. The mirror neuron system in the premotor cortex is thought to play a crucial role in imitation learning (Rizzolatti & Craighero, 2004) as well as in social cognition (Oberman et al., 2005), both represent functions where action observation is crucial. Pineda & Oberman (2006) linked the enhanced mu rhythm to hypersensitivity in the premotor cortex reflecting a probable disconnection of this region from frontal executive networks, which on the other hand might be involved in the development of impulsive and addictive behavior. With respect to the present experiment PG seem to demonstrate a hypersensitivity especially to attractive win situations probably linked to an underlying disconnection of the premotor cortex from frontal areas as a consequence of imitation learning. A crucial point might be that an observed gambling-related action could trigger the own motor representation of that action in the premotor cortex which facilitates imitative learning and empathy for gambling-related behavior.

In addition, bilateral premotor cortex activity was reported to correlate positively with desire of winning a chocolate bar in a wheel of fortune task (Koeneke et al., 2008), which the authors related to enhanced motor preparedness possibly enabling approach behavior. This points to the involvement of the premotor cortex in anticipation of future gambling activity in PG during action-inducing incentive win situations.

Summarizing, higher right superior frontal activity in PG than in OG in the win vs. lose contrast might be related to stronger action selection, motor planning, hypersensitivity to gambling cues, or a consequence of learned behavior facilitating empathy for gambling-related cue-reactivity. Additionally, win situations might function as an incentive for the selection of further gambling activity.

3.4.3.2.4 Summary of regional source activities during reward processing

Altogether, group differences in the win vs. lose comparison have been observed in a frontal-parietal perception-action network in early time windows. Processing of positive vs. negative rewards in PG might be dominated by early strengthened affective stimulus

evaluation in rostral-ventral ACC, coupled with heightened attention at parietal locations, and followed by enhanced imagery, motor planning, and action selection in premotor cortex.

3.4.3.3 Conclusion of the fMRI constrained source analysis

The present experiment combined the high temporal resolution of EEG with good spatial resolution of fMRI which revealed differences between PG and OG during risk assessment and reward processing. During risk assessment, group-specific differences in high-risk vs. low-risk assessment could be characterized in early attentional modulation of frontal and temporal regions in PG, with prolonged stimulus processing in frontal areas. Late group-specific differences might be related to emotional influences of heightened risk processing in PG, which seemed to reflect cue-reactivity to appetitive high-risk gambling situations.
At the moment of reward processing PG and OG differed in the win vs. lose comparison in early time windows, which could be related to cue-induced perception-action cycles. Attention to gambling-related cues might in turn have activated motor planning and action selection in the premotor cortex.

4 General Discussion

The general discussion starts with a short overview of design-specific limitations and shortcomings regarding the integration of fMRI and EEG methods applied in the current thesis. Then, the results of the present dissertation are integrated into the model of Volkow et al. (2003), followed by final conclusions in relation to the core findings of both studies. Finally, perspectives for further research are offered based on the findings obtained in the present thesis to expand these results in PGG research.

4.1 Limitations of the present experiments

Additionally to the mainly group-specific limitations addressed in the discussion sections of experiment 1 and 2 (see final paragraph of chapter 2.4.4 and 3.4.2.3) the next two chapters deal with design-specific shortcomings concerning the integration of fMRI and EEG.

4.1.1 Design-specific limitations

During the start of the game a comparison between different levels of perceived risk might be problematic in relation to the utilized blackjack strategy. The experimental design applied in the present dissertation was conceptualized in such a way that the blackjack basic strategy (Baldwin et al., 1956) advised to draw another card in all low- and high-risk situations. Consequently, on one hand one could assume that on a behavioral level no differences between high- and low-risk should be expected, but on the other hand due to increased risk to get over 21 points by drawing another card both PG and OG behaved more careful in high-risk compared to low-risk situations. This was against observations mostly derived from simple gambling tasks, indicating that PG act more risky than controls (Brand et al., 2005b; Goudriaan et al., 2005). One shortcoming of the present dissertation is that the author did not control whether both groups were equally familiar with the blackjack basic strategy. The obtained results could have been influenced by the possibility that PG might have been more familiar with the basic strategy than OG and actively violated the basic strategy in 30% of the high-risk situations (stand when a hit was proposed). OGs' drawing behavior during high-risk situations (not different from PG; see chapters 2.3.1 and 3.3.1 second paragraph, respectively) might have been spontaneous, not dealing with the basic strategy. Consequently, the found differences on neuronal level

between groups during risk assessment might be related to distinct degrees of uncertainty (Volz et al., 2005) or response conflict (Yang et al., 2007).

Another possible weakness concerning the present design is that although controlled for blackjack frequency, PG might have been more familiar with card games in general. This implicates that OG would have shown slower RT during the start of the game if they had been less familiar with cards. As this was not the case, behavioral data did not indicate differences in familiarity with cards between groups during risk assessment. During reward processing no RT were recorded and, therefore, no inferences about familiarity differences between PG and OG while perceiving a win or a loss could be drawn. It might have still been the case that PG were more skilled in summing up the points of the cards during the end of the game and to conclude whether they won or lost the game. The arithmetic process during reward processing was more difficult than during the start of the game as the players had to sum up their own points (at least three cards) and (in trials were they did not get over the 21) the points of the dealer (at least two cards) before they could anticipate the outcome of a game. An option to avoid this shortcoming would have been to match the PG and OG group for all card gambling activities to rule out differences in arithmetic skills summing up the points of the cards.

In addition, the results of the present dissertation were derived from two samples consisting entirely of male participants. The prevalence of PGG in men was reported to be higher than in women (Shaffer et al., 1999; Welte et al., 2001) and most of the research in PGG is done with male participants. Consequently, it is crucial to mention that one have to be careful in generalizing the obtained results of the present dissertation to female PG as Petry et al. (2005) reported that the reason for gambling in men is assumed to be driven by excitement and thrill-seeking whereas gambling in women was linked to the compensation of bad moods. Nevertheless, the results of the present dissertation during risk assessment are consistent with thrill-seeking in male PG at least on the neuronal level as especially high-risk situations activated neuronal networks in PG, which are reported to be involved in arousal and affective stimulus processing (Bush et al., 2000; Schmahmann, 2003).

4.1.2 Limitations with respect to the integration of fMRI and EEG

Hopfinger et al. (2005) proposed four important aspects for a combined EEG/fMRI approach. First, the experimental frame such as timing, instructions and participants' expectations should be identical. Second, in both experiments the same stimuli should be

used. Third, both experiments should use identical spatial reference e.g. Talairach space. Fourth, there should be the same participants in both studies (identical biological reference). As a consequence of this, one weak point regarding the fMRI constrained source analysis in the present thesis is that data from fMRI and EEG were recorded from a different sample of participants. It would have improved accuracy between additional fitted and fMRI constrained sources by recording fMRI and EEG from the same sample. Nevertheless, in the fMRI constrained source analysis implemented in the present study, three out of four aspects were met and hence warranted the present source analysis approach.

Separate source models for start and end of the game were applied on difference waves between conditions of the single individual data and then statistically compared between PG and OG. This procedure revealed information about group-specific differences between distinct levels of risk and rewards with the consequence that a comparison between groups on a single risk or reward condition was not feasible anymore. An alternative approach would have been to develop a source model on basis of a fMRI contrast over all conditions vs. baseline (low level baseline/fill-trials see chapter 2.2.3 first paragraph) and then applying this model on the individual ERPs per condition. The reason for working with difference waves between conditions was that the integrative approach of the fMRI constrained source analysis had to be based on the results of the fMRI contrasts obtained in experiment 1, aiming at a comparison of different levels of perceived risk and reward levels (see also chapter 1.6 first paragraph).

Furthermore, source analysis results of the ACC and thalamus must be interpreted with caution since deep located sources can sum up to invalidly high source waveform amplitudes through picking up activity from surrounding brain regions (Im, 2007). Both thalamus and ACC demonstrated indeed a strong amplitude increase over time (see appendix A 17 RS3 and A 18 RS3). Yet, both sources were included in the model as the thalamus source was derived from the fMRI study and the ACC source showed differences between groups in an early time window where its deflection had still an acceptable amplitude. In addition, both sources participated considerably in decreasing the residual variance of the source models.

On one hand, seeding sources based on prior knowledge of the fMRI study (Bledowski et al., 2006) is more objective as it is avoiding a wrong number and a wrong starting position of seeded sources (Luck, 2005). However, in the present dissertation most of the sources were additionally fitted (6 of 9 RS for the start and 9 of 11 RS for the end of the game)

and, therefore, prone to selecting the wrong starting position and the wrong number of sources.

On the other hand, a general problem with respect to fMRI constrained source analysis with BESA was reported by Luck (2005) who claimed that there is a possible confirmation bias in the sense that expected results will be accepted although they might be incorrect. In the source analyses of the present thesis only few fMRI constrained sources were incorporated in the source models (3 of 9 RS for the start and 2 of 11 RS for the end of the game) and for that reason vulnerability to this bias was limited. Consequently, the applied combination of fMRI constrained and additionally fitted sources tried to deal with both problems mentioned above.

Im (2007) proposed three types of mismatches between fMRI and sources obtained by EEG source analysis. First, fMRI extra sources visible in fMRI but not in EEG e.g. deep close field sources, with weak detectable signal outside of the scalp surface. Second, fMRI invisible sources exclusively visible in EEG, like brain activity short in time, which is not detected with fMRI as this method integrates neuronal activity over time. Third, fMRI discrepancy sources due to basal differences between EEG and fMRI technique, such as temporal (Liu & He, 2008) and spatial resolution (Disbrow et al., 2000). As in the present dissertation sources from the fMRI study were combined with additionally fitted sources, the obtained source model comprised discrepancy sources due to differences between fMRI and EEG methods. In addition, particularly fMRI invisible sources were successfully incorporated in the fMRI constrained source models of the present experiment because additionally fitted sources led to a substantial decrease in residual variances of both models.

To conclude, additionally fitted sources improved the source analysis models for the start and the end of the game, which legitimated a hybrid approach for the combination of fMRI and EEG technique. Nevertheless, concerning the exploratory character of the fMRI constrained source analyses reported in this thesis, further studies should replicate spatio-temporal patterns of neuronal activity in PG during risk assessment and reward processing within an ecological valid experimental environment.

4.2 Integration of the results in the model of Volkow et al. (2003)

The model of Volkow et al. (2003) introduced in the first chapter (see Figure 1.1) proposed a network of four circuits probably involved in drug abuse and addiction. First, the reward

circuit with the NAc and ventral pallidum as core structures is thought to be related to the salience of a stimuli or to reinforcing effects of a drug, linked to enhanced extracellular DA concentration. Second, the motivation/drive circuit, with OFC as assumed main structure, where signal increase is proposed to be related to heightened intensity of drug-induced craving and compulsivity. Third, the circuit of memory and learning which is suggested to be subdivided in conditioned incentive learning modulated by the NAc and amygdala, habit learning partly processed in nucleus caudatus and putamen, and declarative memory modulated by the hippocampus. Incentive learning is thought to be important in coupling a neutral stimulus with the drug which leads to motivational salience of this stimulus. Habit learning activates learned behavioral sequences automatically, and declarative memory links emotionally states to drug consumption. Finally, a control circuit thought to be involved in risk assessment/decision making and inhibitory control with PFC and ACC as core locations.

The obtained results from source analysis of the present thesis showed that high-risk vs. low-risk assessment was accompanied by heightened source strength primarily in orbitofrontal and thalamic regions in PG compared to OG. During the end of the blackjack game reward processing in the win vs. lose comparison was dominated by early rostral-ventral ACC activity coupled with parietal-premotor activation exclusively in PG.

Consequently, one can speculate about a general weakened processing within the control circuit of PG coupled to an enhancement of their motivation/drive circuit. The PFC engaged in response inhibition and the dorsal ACC involved in conflict/performance monitoring (Botvinick et al., 2004) as important components of the control circuit in healthy persons might have undergone an activation shift to OFC and rostral-ventral ACC in PG, both core members of the motivation/drive circuit with a strong affective attribute (Bush et al., 2000). In terms of the somatic marker hypothesis (Bechara, 2005) raised in the introduction (see chapter 1.5) results of the present dissertation might indicate that the reflective PFC system, involved in processing future prospects in healthy persons, switched to process immediate, emotion-related prospects in PG.

During high-risk vs. low-risk assessment source analysis revealed that differences between neuronal responses of PG and OG were indicated by early cue-driven attentional operations, followed by enhanced arousal-related thalamic and affective orbitofrontal processing. This provides support for a heightened activity of the motivation/drive circuit fostered by early selective attentional processing. Neuronal activity during reward processing was characterized by early prolonged rostral-ventral ACC activity in PG when

compared to OG in the win vs. lose contrast, which might again point to activity within the motivation/drive circuit. In addition, activation of a perception-action-related (Prinz, 1997) parietal-prefrontal network (Fuster, 2006; Quintana & Fuster, 1999; Schnell et al., 2007; van Eimeren et al., 2006) in the P3b time window might support preparatory compulsive activity in PG after winning money, which could be driven by early affective ACC involvement (Bush et al., 2000; Mohanty et al., 2007; Quintana & Fuster, 1999).

Further evidence for the affective/emotional involvement in PGG comes from results of the first experiment of this dissertation. It was reported that during low-risk vs. high-risk assessment in OG compared to PG similar regions were active as in the reverse contrast (high-risk vs. low-risk) when comparing PG to OG (see Table 2.2) - with one exception. Throughout low-risk assessment OG did not show inferior/orbitofrontal activation enhancement relative to the high-risk situation, whereas PG clearly demonstrated this effect during the reverse contrast. This result might refer to a group-specific affective involvement during risk assessment exclusively in PG, whereas both groups showed arousal-related thalamic activations. Therefore, high-risk assessment in PG seemed to be characterized by arousal- and affect-related processing within the motivation/drive circuit, whilst OG might simply have demonstrated arousal-related activation in low-risk situations.

The fact that there were no significant group differences in brain regions associated with the circuits of learning/memory and reward might be attributed to the possibility that on one hand these circuits are particularly involved during the acquisition of PGG in the transitions from reward based incentive learning to habit or compulsive behavior (Brewer & Potenza, 2008; Everitt & Robbins, 2005) potentially related to changes in the opioid/endorphin system (Shinohara et al., 1999; see also chapter 1.2.4). On the other hand, the circuits of learning/memory and reward might have demonstrated high activity in both groups but did not lead to observable neuronal differences between them due to the complexity of the experimental task, as e.g. both PG and OG had to hold the sum of the cards in working memory during the start and end of the game to prepare a decision and to realize a win or a loss. Additionally, the general observed weakened reward processing in daily situations in PG (Goldstein & Volkow, 2002) might have been raised to a “normal level” by the addiction-related nature of the task, yielding no group differences within the reward circuit.

To summarize, according to the model of Volkow et al. (2003) PGG seems to be characterized by strengthened involvement of the addiction memory powered

motivation/drive circuit which might have detracted activity from the control/conflict circuit especially during high-risk assessment and winning money. Accordingly, this might point to a discrepancy between "rational" risk and reward processing in healthy persons and placing emphasis on affective, compulsive attribution of these processes in PG (Brewer & Potenza, 2008), possibly driven by heightened salience of conditioned gambling-related cues (McClernon et al., 2009). One could speculate whether activity in the affective motivation/drive circuit in PG, particularly during appetitive high-risk and win situations, might be affiliated with serotonin-induced euphoric enhancement (Pallanti et al., 2006).

4.3 Final conclusions

The present dissertation is one of the first studies combining EEG and fMRI technique and applying an ecological valid design to explore PGG-specific networks during both risk assessment and reward processing.

The goal of experiment 1 was to analyze the BOLD response related to both risk assessment and reward processing in PGG within an ecologically valid quasi-realistic blackjack game. High-risk situations in PG as well as low-risk situations in OG strengthened the BOLD response in similar arousal-related brain networks. During reward processing both groups did not differ regarding to their activity in the NAc, whereas PG exclusively showed activity in a parietal-premotor network probably related to cue-induced perception-action cycles.

Experiment 2 aimed at characterizing the temporal dynamics of risk assessment and reward processing using EEG technique within an identical experimental design as in experiment 1. The enhanced P3b and LPP amplitude in PG during the high-risk vs. low-risk comparison pointed to heightened task relevance of high-risk situations coupled with strengthened arousal and craving. Winning money in PG was accompanied by early attention-related frontal N1 enhancement, and followed by heightened fronto-parietal generated intensity processing in the P3b time-window.

fMRI constrained source analysis combined the results of fMRI and EEG studies and revealed a more detailed picture of PGG disorder by focusing on group differences between successively activated brain regions over time throughout both phases of the blackjack game.

During high-risk vs. low-risk assessment (start of the game) PG demonstrated early attention-related temporal and affect-associated orbitofrontal modulations with prolonged stimulus processing in frontal areas. This was followed by enhanced activity in a superior and orbitofrontal, temporal, and thalamic network in PG, probably related to cue-reactivity. At the moment of reward processing when comparing winning vs. losing money PG showed strengthened early transient parietal and sustained ACC activity, followed by enhanced superior frontal source activity when compared to OG, which might reflect modulations in perception-action cycles driven by gambling cues.

Altogether, high-risk as well as win situations seem to be important in the development and maintenance of PGG owing to their proposed function as central gambling cues. Both rostral-ventral ACC and OFC seem to play a key role in these processes through their involvement in the integration of emotional value of rewards, expectancy, and decision making (Kringelbach, 2005).

4.4 Perspectives for further research

While the analysis of the data revealed by the present experiments concentrated on group-specific differences within risk assessment and reward processing it would be interesting to have a closer look on successive effects during the blackjack game in future experiments. For example future analyses will on one hand have to explore whether there are differences between groups when comparing high-risk and low-risk situations preceded by wins vs. losses. This might shed light on addiction-specific dynamics within a gambling situation. It would be possible, to examine whether groups deal differently with transferring outcome-related information while making a risk-dependent decision. This approach might be appropriate in revealing neuronal correlates of trait differences between PG and OG in a gambling situation, as it could be assumed that PG generally behave more impulsive than OG (Blanco et al., 2009) especially during risk assessment/decision making after losses. On the other hand, an interesting focus of research would be to analyze differences between groups when comparing wins and losses within high-risk vs. low-risk situations. In this context it will be crucial to control for the individual drawing behavior of the participant (no group differences in hit/stand ratio in high-risk-win, high-risk-lose, low-risk-win, and low-risk-lose trials). The inclusion of validity and fill conditions in the present experimental design diminished the number of trials for analyzing of successive effects to an amount that would have made ERP comparisons problematic. Future designs

will have to consider a removal of a baseline condition to raise the number of successive trial conditions, suitable for statistical comparisons.

Additionally, upcoming PGG research should aim at extending methodological or design-specific approaches. It would be interesting to apply time-frequency analysis on EEG data to gain a closer look on dominant frequency bands of brain-signals over time (Makeig, 1993). Consequently, one would be able to relate findings about oscillatory activity during reward processing reported in healthy persons (Kamarajan et al., 2008; Marco-Pallares et al., 2008) to PG. Alternatively, one could focus on the neuronal activity of PG during economic decisions. This could be tested on a more neutral paradigm sensitive to impulsivity levels of participants to gain insight about underlying neuronal correlates of elevated discount rates of delayed rewards observed in PG (Kirby et al., 1999; Petry, 2001). Therefore, results gained within this line of research would provide valuable information about general problems of PG in everyday decision making closely connected to possible consequences on contractual capability.

Further research should also try to extend the present experiment by testing additional groups of participants. Incorporating a third group of persons suffering from another addiction or impulse control disorder in a new experiment with the same design could answer the question whether the reported effects were exclusively PGG-related. Additionally, this approach would provide further insights concerning an appropriate classification of PGG in relation to impulse control disorders and substance addictions. Another research strategy could focus on a specific group of PG being homogeneous regarding their preferred gamble. E.g. slot machine gamblers should be tested in a “real slot machine situation”, where parameters like event frequency and levels of risk could be manipulated separately to obtain a more detailed picture of the neuronal responses underlying or driving a specific PGG problem. Finally, including a group of female PG would expand the present findings concerning possible gender differences.

Based on the reported findings of the present dissertation some of the ideas proposed in this chapter should be incorporated in future experiments to refine knowledge about neurobiological correlates of PGG.

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Appendix

A 1 Information form on fMRI study (next 2 pages).

Informationsblatt für Probanden

Sehr geehrte Probandin, sehr geehrter Proband,

vielen Dank für Ihr Interesse an einer Studie, bei der die Aktivität im Gehirn während des Glücksspiels untersucht werden soll. Wir möchten Sie zunächst über den Ablauf informieren, um Ihnen einen Überblick über die geplanten Messungen zu ermöglichen und Ihnen das Ziel der Untersuchung zu erklären. Die Untersuchungen werden mit einem Magnetresonanztomographen (kurz MRT) durchgeführt, der uns Messungen der Durchblutung im Gehirn schmerzfrei und ohne zusätzliche Gabe von Medikamenten ermöglicht. Einige Personen werden die Untersuchung schon einmal erlebt haben, wenn hochauflösende Bilder vom Kopf im Rahmen der Diagnostik durchgeführt wurden.

Ziel der Untersuchung

Die Studie soll die Aktivität im Gehirn während der Durchführung eines visuell präsentierten BlackJack-Spiels bestimmen.

Was ist eine Magnetresonanztomographie?

Im Rahmen der Studie ist eine funktionelle Magnetresonanztomographie des Gehirns vorgesehen. Mit Hilfe dieser Methode ist es möglich, die Durchblutung in Ihrem Gehirn zu messen und daraus Rückschlüsse auf die bei der Aufgabe beteiligten Bereiche zu ziehen. Hierbei treffen Radiowellen, die in dem Magnetfeld erzeugt worden sind, auf den Körper, der Signale zurückschickt. Diese Echosignale werden von speziellen Antennen aufgefangen und in einem Computer ausgewertet.
Ein Kontrastmittel ist **n i c h t** erforderlich. Es werden **k e i n e** Röntgenstrahlen eingesetzt.

Wie läuft die Untersuchung ab?

Vor der Untersuchung werden Sie vom Untersuchungsleiter ausführlich über die für den Tag geplanten Messungen und Ziele informiert. Sie haben das Recht, ohne Angabe von Gründen die Teilnahme an der Messung abzulehnen. Auch im Verlauf der Untersuchung werden Sie vom Untersucher jederzeit gehört.
Für die Untersuchung müssen Sie sich auf eine Liege legen. Im Meßbereich wird eine Kopfspule angebracht. Mit der Liege werden Sie dann langsam in die Röhre des Kernspintomographen geschoben. Dort befinden Sie sich während der gesamten Untersuchung, die normalerweise 60 Minuten dauert, in einem starken Magnetfeld, das für die Untersuchung benötigt wird. Während der eigentlichen Messung sind sehr laute Klopfgeräusche zu hören, die völlig normal sind und von elektromagnetischen Schaltungen herrühren. Das Magnetfeld selbst können Sie weder spüren noch hören. Es ist für die Qualität der Messungen von großer Bedeutung, dass Sie während der Untersuchung möglichst ruhig liegen bleiben. Um dies zu erleichtern, werden Ihr Kopf und Arme mit Polstern und anderen Hilfsmitteln schmerzfrei gelagert. Die Aufgaben, die Sie während der Untersuchung zu bearbeiten haben, werden Ihnen über einen an der Kopfspule angebrachten Spiegel dargeboten.

Mögliche Risiken der Methode?

Der Kernspintomograph hält alle für die Sicherheit des Betriebes und insbesondere die Sicherheit der Probanden/Patienten erforderlichen Grenzwerte ein. Er wurde vom TÜV einer Sicherheitsprüfung unterzogen und wird darüber hinaus in den vorgeschriebenen Intervallen überprüft. Dennoch müssen folgende Punkte beachtet werden.

1. Auf ferromagnetische Gegenstände (z.B. Gegenstände, die Eisen oder Nickel enthalten) im Bereich des Magneten (z.B. Messer, Schraubenzieher, Kugelschreiber, Münzen, Haarspangen, Piercings, Ohrringe ..) wird eine starke Anziehungskraft ausgeübt. Dadurch werden die Gegenstände mit großer Geschwindigkeit in den Magneten gezogen und können Personen erheblich verletzen.
2. Metallkörper und andere Fremdkörper wie Geschoßteile können ebenfalls ferromagnetisch sein, durch magnetische Kräfte ihre Position im Körper verändern und dadurch innere Verletzungen hervorrufen.
3. Kleine Metallsplitter im Auge können durch magnetische Kräfte bewegt oder gedreht werden und das Auge verletzen.
4. Personen mit Chochlea-Implantaten, Defibrillatoren oder Pumpensystemen sollten nicht einem starken Magnetfeld ausgesetzt werden, da es auch in diesen Fällen zu Risiken durch magnetische Kräfte kommen kann.
5. Herzschrittmacher können im Magnetfeld ihre Funktionsfähigkeit verlieren. Deshalb dürfen Personen mit Herzschrittmachern nicht an Untersuchungen teilnehmen.
6. Bei der Messung mit dem Kernspintomographen kommt es zur Abstrahlung von hochfrequenter elektromagnetischer Strahlung, wie sie z.B. bei Radiosendern und Funktelefonen auftritt. Dies kann zu einer geringfügigen Erwärmung des untersuchten Gewebes führen.
7. Das Schalten der Magnetfeldgradienten führt in Teilen des Gradientensystems zu mechanischen Verformungen, die Geräusche mit Lautstärken über 100 dB erzeugen können. Deshalb müssen Sie bei allen Messungen entweder schallabsorbierende Kopfhörer oder Lärmschutzstopfen tragen, die von uns zur Verfügung gestellt werden. Bei Einhaltung dieser Vorsichtsmaßnahmen kann eine Schädigung des Hörsystems ausgeschlossen werden.
8. Manche Menschen erleben enge Räume als bedrohlich. Sie berichten über Unwohlsein z.B. in Fahrstühlen oder in großen Menschenansammlungen. Obwohl diese Angsterkrankung meist über die Anamnese ausgeschlossen werden kann, ist ein erstmaliges Auftreten während der Messung im Kernspintomographen möglich. Der Untersucher ist bei der Messung anwesend; bei dem Auftreten von Symptomen kann der Proband über Sprechkontakt bzw. über eine Notklingel jederzeit auf sich aufmerksam machen, so dass bei Symptomen eine rasche Intervention gewährleistet ist.

A 2 Questionnaire with exclusion criteria for fMRI measurements.

Fragebogen für Teilnehmer/innen an Kernspinresonanzuntersuchungen

Name:.....
Vorname:.....Geschlecht:.....
Geburtsdatum:.....
Straße/Hausnummer:.....
Wohnort:.....
Telefon:.....
Beruf:.....

Beantworten Sie bitte folgende Fragen zu möglichen Gegenanzeigen für Ihre Teilnahme an den Untersuchungen (Zutreffendes unterstreichen):

Sind Sie Träger eines Herzschrittmachers oder anderer elektrischer Geräte?	□ ja	□ weiß nicht	□ nein
Besitzen Sie metallische Implantate (z.B. Zahnschrauben oder metallische, mechanische Verhütungsmittel)?	□ ja	□ weiß nicht	□ nein
Befinden sich in Ihrem Körper andere metallische Fremdkörper?	□ ja	□ weiß nicht	□ nein
Wurde bei Ihnen eine Gefäßoperation durchgeführt?	□ ja	□ weiß nicht	□ nein
Haben Sie eine Allergie gegen Medikamente	□ ja	□ weiß nicht	□ nein
Haben Sie Piercings oder Tätowierungen?	□ ja	□ weiß nicht	□ nein
Leiden Sie unter Platzangst?	□ ja	□ weiß nicht	□ nein
Sind bei Ihnen oder in Ihrer Familie Anfallsleiden (Epilepsie, Fallsucht) aufgetreten?	□ ja	□ weiß nicht	□ nein
Besteht die Möglichkeit, dass Sie schwanger sind?	□ ja	□ weiß nicht	□ nein

Beantworten Sie bitte folgende für unsere Untersuchungen wichtigen Fragen:

Sind Sie linkshändig oder rechtshändig?	□ ja	□ weiß nicht	□ nein
Sind Sie Brillenträger/in?	□ ja	□ weiß nicht	□ nein
Tragen Sie Kontaktlinsen?	□ ja	□ weiß nicht	□ nein
Haben Sie Hörprobleme?	□ ja	□ weiß nicht	□ nein
Sind Sie mehrsprachig aufgewachsen?	□ ja	□ weiß nicht	□ nein

Ich habe alle Fragen auf dieser Seite wahrheitsgemäß und nach bestem Wissen beantwortet.

_____ _____

Ort, Datum Unterschrift der Probandin/des Probanden

A 3 Consent form for fMRI measurements.

Einwilligungserklärung

Über die geplante kernspintomographische Untersuchung im Rahmen einer wissenschaftlichen Studie hat mich Frau / Herr ..... in einem Aufklärungsgespräch ausführlich informiert. Auch habe ich das entsprechende Informationsblatt gelesen und den Fragebogen zu möglichen Ausschlusskriterien ausgefüllt.
Ich konnte alle mir wichtig erscheinenden Fragen, z.B. über die in meinem Fall speziellen Risiken und möglichen Komplikationen und über die Neben- und Folgemaßnahmen stellen, die zur Vorbereitung oder während der Untersuchung erforderlich sind.

Die mir erteilten Informationen habe ich inhaltlich verstanden. Mir ist bekannt, dass ich meine Einwilligung jederzeit ohne Angaben von Gründen widerrufen kann.
Ich weiß, dass die bei Untersuchungen mit mir gewonnenen Daten auf der Basis elektronischer Datenverarbeitung weiterverarbeitet und eventuell für wissenschaftliche Veröffentlichungen verwendet werden sollen.
Ich bin mit der anonymisierten Verarbeitung und Veröffentlichung dieser Daten einverstanden. Auch diese Einwilligung kann ich jederzeit ohne Angabe von Gründen widerrufen.

Ich gebe hiermit meine Einwilligung, dass bei mir im Rahmen eines Forschungsvorhabens eine Kernspintomographie des Gehirns durchgeführt wird.

Ich erkläre mich damit einverstanden, dass meine persönlichen Daten in einer für die Öffentlichkeit nicht zugänglichen Datenbank erfasst werden. Die Speicherung meiner Daten dient ausschließlich der Möglichkeit einer erneuten Kontaktaufnahme des Instituts zum Zwecke der Vereinbarung weiterer Untersuchungen.
Informationen zu meiner Person werden im Rahmen datenschutzrechtlicher Bedingungen verwaltet.

_____	_____	_____
Ort, Datum	Unterschrift Proband/in	Unterschrift Untersucher

PROBANDENCODE:_____

A 4 Information form on EEG study.

Informationsblatt für Probanden

Sehr geehrte Probandin, sehr geehrter Proband,

vielen Dank für Ihr Interesse an einer Studie, bei der die Aktivität im Gehirn während des BlackJack-Spiels untersucht werden soll.

Wir möchten Sie zunächst über den Ablauf informieren, um Ihnen einen Überblick über die geplanten Messungen zu ermöglichen und Ihnen das Ziel der Untersuchung zu erklären. Die Untersuchungen werden mit Hilfe der Elektroenzephalographie (kurz EEG) durchgeführt, die Messungen der Nervenzell-Aktivität im Gehirn ohne Eingriff, schmerzfrei und ohne zusätzliche Gabe von Medikamenten ermöglicht.

Ziel der Untersuchung

Die Studie soll die Aktivität im Gehirn während der Durchführung einer visuell präsentierten Aufgabe bestimmen.

Was ist ein Elektroenzephalogramm (EEG)?

Aufgrund der Aktivität der Nervenzellen lässt sich an der Kopfoberfläche fortlaufend eine elektrische Spannung messen – das Elektroenzephalogramm (EEG). Für die EEG-Messung müssen an verschiedenen Stellen des Kopfes Elektroden platziert werden, die eine Verbindung zwischen Kopfoberfläche und Messgerät herstellen.

Die Elektroden bestehen aus Silber/Silberchlorid, Zinn oder Gold. Zur Verbesserung der Leitfähigkeit wird eine Paste verwendet, die im Wesentlichen aus Wasser, Kochsalz und Verdickungsmittel besteht. Um zwischen Haut und Elektrode einen hinreichend guten Kontakt herzustellen, werden die Elektroden an einer speziellen Haube, ähnlich einer Badekappe, fixiert.

Wie läuft die Untersuchung ab?

Vor der Untersuchung werden Sie vom Untersuchungsleiter ausführlich über die für den Tag geplanten Messungen und Ziele informiert. Sie haben das Recht, jederzeit ohne Angabe von Gründen und ohne persönlichen Nachteil, die Teilnahme an der Messung abzulehnen oder während der Messung abzubrechen.

Während der Messung sitzen Sie auf einem Stuhl. Um Störungen der Messung zu vermeiden, findet die Untersuchung in einem eigenen, abgeschirmten und störungsarmen Raum statt. Während der Messung sind Sie zusammen mit einem Mitarbeiter der Abteilung in einem Raum und können sich jederzeit an ihn wenden.

Mögliche Risiken der Methode?

Die EEG-Messung ist vollständig gefahrlos. Für das EEG werden nur solche Geräte verwendet, die den einschlägigen Sicherheitsbestimmungen genügen. Sie werden in gleicher Form auch für die klinische Routine eingesetzt.

A 5 Consent form for EEG measurements.

Einwilligungserklärung

Über die geplante EEG-Untersuchung im Rahmen einer wissenschaftlichen Studie hat mich Frau / Herr ..... in einem Aufklärungsgespräch ausführlich informiert. Auch habe ich das entsprechende Informationsblatt gelesen und den Fragebogen zu möglichen Ausschlusskriterien ausgefüllt.
Ich konnte alle mir wichtig erscheinenden Fragen, z.B. über die in meinem Fall speziellen Risiken und möglichen Komplikationen und über die Neben- und Folgemaßnahmen stellen, die zur Vorbereitung oder während der Untersuchung erforderlich sind.

Die mir erteilten Informationen habe ich inhaltlich verstanden. Mir ist bekannt, dass ich meine Einwilligung jederzeit ohne Angaben von Gründen widerrufen kann.
Ich weiß, dass die bei Untersuchungen mit mir gewonnenen Daten auf der Basis elektronischer Datenverarbeitung weiterverarbeitet und eventuell für wissenschaftliche Veröffentlichungen verwendet werden sollen.
Ich bin mit der anonymisierten Verarbeitung und Veröffentlichung dieser Daten einverstanden. Auch diese Einwilligung kann ich jederzeit ohne Angabe von Gründen widerrufen.

Ich gebe hiermit meine Einwilligung, dass bei mir im Rahmen eines Forschungsvorhabens eine EEG-Untersuchung durchgeführt wird.

Ich erkläre mich damit einverstanden, dass meine persönlichen Daten in einer für die Öffentlichkeit nicht zugänglichen Datenbank erfasst werden. Die Speicherung meiner Daten dient ausschließlich der Möglichkeit einer erneuten Kontaktaufnahme des Instituts zum Zwecke der Vereinbarung weiterer Untersuchungen.
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_____	_____	_____
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PROBANDENCODE:_____

A 6 DSM 4 questionnaire for the diagnosis of pathological gambling.

Beachten Sie, bei den Fragen im nachfolgenden Kasten geht es ums **Glücksspiel im Allgemeinen, einschließlich Pokern und andere Glücksspiele im Internet.**

Denken Sie bei der Beantwortung der Fragen an die Zeitspanne der **letzten 12 Monate.**

	In den letzten 12 Monaten	
	ja	nein
16. Gab es Zeiten, in denen Sie sehr häufig an vergangene Spielerfahrungen oder die Planungen zukünftiger Spielaktivitäten gedacht haben oder daran, wie Sie Ihr Glücksspiel finanzieren könnten?	O	O
17. Haben Sie jemals das Bedürfnis verspürt, mit höheren Einsätzen zu spielen, um die gewünschte Erregung zu erzielen?	O	O
18. Haben Sie wiederholt erfolglos versucht, Ihre Teilnahme am Glücksspiel zu kontrollieren, einzuschränken oder aufzugeben?	O	O
19. Fühlen Sie sich bei dem Versuch, das Glücksspiel einzuschränken oder ganz aufzugeben, unruhig oder gereizt?	O	O
20. Haben Sie gespielt, um persönlichen Problemen auszuweichen oder um unangenehme Gefühle wie Hilflosigkeit, Schuld, Angst oder Depressionen abzubauen?	O	O
21. Haben Sie nach Verlusten beim Glücksspiel oft den Versuch unternommen, diese Verluste durch erneutes Spiel wieder auszugleichen?	O	O
22. Haben Sie Familienmitglieder, Therapeuten oder andere Personen angelogen, um das Spielen zu verheimlichen?	O	O
23. Haben Sie illegale Handlungen wie Fälschung, Betrug, Diebstahl oder Unterschlagung begangen, um das Glücksspiel zu finanzieren oder Spielschulden zu begleichen?	O	O
24. Haben Sie wegen des Glücksspiel eine wichtige Beziehung, den Arbeits-/ Ausbildungsplatz oder berufliche Aufstiegschancen gefährdet oder verloren?	O	O
25. Haben Sie sich darauf verlassen, dass andere Personen Ihre Spielschulden begleichen oder Ihre spielbedingten finanziellen Probleme lösen?	O	O

A 7 Kurzfragebogen zum Glücksspielverhalten (KFG) questionnaire for the diagnosis of pathological gambling.

Kurzfragebogen zum Glücksspielverhalten (KFG)

(Petry & Baulig)

VP-NR.: _____

Sie lesen jetzt eine Reihe von Aussagen zum Glücksspielverhalten in Ihrem Leben. Falls Sie zur Zeit nicht spielen, beziehen Sie sich bitte auf vergangene Spielphasen. Bitte Beurteilen Sie zu **jeder** dieser Aussagen, ob diese auf Sie entweder **‚gar nicht zutrifft'**, **‚eher nicht zutrifft'**, **‚eher zutrifft'**, oder **‚genau zutrifft'**. Machen Sie ein Kreuz in das entsprechende Kästchen. Bitte **bearbeiten Sie alle Aussagen** und wählen Sie jeweils **nur eine** der vorgegebenen Antwortmöglichkeiten.

	trifft gar nicht zu	trifft eher nicht zu	trifft eher zu	trifft genau zu
01 Ich habe meistens gespielt, um den Verlust wieder auszugleichen.				
02 Ich kann mein Spielen nicht mehr kontrollieren.				
03 Meine Angehörigen oder Freunde dürfen nicht wissen, wieviel ich verspiele.				
04 Im Vergleich zum Spielen erscheint mir der Alltag langweilig.				
05 Nach dem Spielen habe ich oft ein schlechtes Gewissen.				
06 Ich benutze Vorwände, um spielen zu können.				
07 Ich schaffe es nicht, das Spielen längere Zeit einzustellen.				
08 Ich spiele fast täglich um Geld.				
09 Durch mein Spielen habe ich berufliche Schwierigkeiten.				
10 Beim Spielen suche ich Nervenkitzel.				
11 Ich denke ständig ans Spielen.				
12 Um mein Spiel zu finanzieren, habe ich oft unrechtmäßig Geld besorgt.				
13 Den größten Teil meiner Freizeit spiele ich.				
14 Ich habe schon fremdes bzw. geliehenes Geld verspielt.				
15 Ich war wegen meiner Spielprobleme schon in Behandlung.				
16 Ich habe häufig mit dem Spielen aufhören müssen, weil ich kein Geld mehr hatte.				
17 Weil ich so viel spiele, habe ich viele Freunde verloren.				
18 Um spielen zu können, leihe ich mir häufig Geld.				
19 In meiner Phantasie bin ich der große Gewinner.				
20 Wegen des Spielens war ich schon oft so verzweifelt, daß ich mir das Leben nehmen wollte.				

A 8 South Oaks Gambling Screen (SOGS) questionnaire for the diagnosis of pathological gambling (next 3 pages).

South Oaks Gambling Screen (SOGS) -

1. Bitte kreuzen Sie an, an welchen der unten genannten Spielarten Sie in Ihrem Leben teilgenommen haben. Markieren Sie für jede Spielart eine Antwort: "niemals", "weniger als einmal pro Woche" oder "ein bis mehrmals pro Woche".

Karten spielen um Geld:
☐ niemals ☐ weniger als 1x pro Woche ☐ 1 bis mehrmals pro Woche

Pferdewetten, Hunde- oder Tierwetten (vor Ort, über Buchmacher o.Ä.):
☐ niemals ☐ weniger als 1x pro Woche ☐ 1 bis mehrmals pro Woche

Sportwetten:
☐ niemals ☐ weniger als 1x pro Woche ☐ 1 bis mehrmals pro Woche

Würfelspiele um Geld:
☐ niemals ☐ weniger als 1x pro Woche ☐ 1 bis mehrmals pro Woche

Spiele im Kasino (legal oder illegal):
☐ niemals ☐ weniger als 1x pro Woche ☐ 1 bis mehrmals pro Woche

Lotterie- oder Totospiele:
☐ niemals ☐ weniger als 1x pro Woche ☐ 1 bis mehrmals pro Woche

Bingo um Geld:
☐ niemals ☐ weniger als 1x pro Woche ☐ 1 bis mehrmals pro Woche

Spiele an Börse oder auf dem Optionsmarkt:
☐ niemals ☐ weniger als 1x pro Woche ☐ 1 bis mehrmals pro Woche

Geldautomatenspiele jeglicher Art:
☐ niemals ☐ weniger als 1x pro Woche ☐ 1 bis mehrmals pro Woche

Geschicklichkeitsspiele (z.B. Bowling, Billard, Golf,...) mit Geldeinsatz:
☐ niemals ☐ weniger als 1x pro Woche ☐ 1 bis mehrmals pro Woche

Rubbellotterien oder andere "Papierspiele":
☐ niemals ☐ weniger als 1x pro Woche ☐ 1 bis mehrmals pro Woche

Andere Spielarten, die hier nicht aufgelistet sind:
☐ niemals ☐ weniger als 1x pro Woche ☐ 1 bis mehrmals pro Woche

2. Welche ist die höchste Summe, mit der Sie jemals an einem Tag gespielt haben?
☐ ich habe nie gespielt
☐ 10 Euro oder weniger
☐ mehr als 10 und bis zu 100 Euro
☐ mehr als 100 und bis zu 1000 Euro
☐ mehr als 1000 und bis zu 10 000 Euro

3. Überprüfen und markieren Sie, welche der folgenden Menschen aus Ihrem Leben ein Spielproblem haben (oder hatten):

- ☐ Vater
- ☐ Mutter
- ☐ Großvater/-mutter
- ☐ Bruder oder Schwester
- ☐ Ehe- oder Lebenspartner
- ☐ meine Kinder
- ☐ andere Verwandte
- ☐ ein(e) Freund(in)
- ☐ ein anderer wichtiger Mensch aus meinem Leben

4. Wenn Sie spielen, wie häufig versuchen Sie an einem der nächsten Tage durch erneutes Spielen Geldverluste zurückzugewinnen?

- ☐ niemals
- ☐ manchmal (weniger als die Hälfte der Male, bei denen ich Geld verloren habe)
- ☐ bei Geldverlusten meistens
- ☐ immer nach Geldverlusten

5. Haben Sie jemals behauptet, dass Sie beim Spielen Geld gewonnen haben, obwohl Sie in Wirklichkeit verloren hatten?

- ☐ niemals
- ☐ ja, weniger als die Hälfte der Male, bei denen ich verloren hatte
- ☐ ja, meistens

6. Haben Sie den Eindruck, Sie hatten jemals ein Problem mit Geldwetten oder Geldspielen?

- ☐ nein
- ☐ ja, in der Vergangenheit, aber nicht jetzt
- ☐ ja

7. Haben Sie jemals mehr gespielt, als Sie beabsichtigt hatten?

- ☐ ja
- ☐ nein

8. Haben andere Menschen Ihr Wettverhalten kritisiert oder Ihnen gesagt, Sie hätten ein Spielproblem, unabhängig davon, ob Sie dem zustimmten oder nicht?

- ☐ ja
- ☐ nein

9. Haben Sie sich jemals schuldig gefühlt in Bezug auf die Art, wie Sie spielen oder was passiert, wenn Sie spielen?

- ☐ ja
- ☐ nein

10. Hatten Sie jemals den Wunsch, mit dem Spielen oder Wetten aufzuhören, fühlten sich aber gleichzeitig unfähig dazu?

☐ ja
☐ nein

11. Haben Sie jemals Spielbelege, Lotterietickets, Spielgeld, Schuldscheine oder andere Anzeichen für Wetten oder Spielen vor Ihrem Ehe-/Lebenspartner, Ihren Kindern oder anderen wichtigen Personen aus Ihrem Leben versteckt?

☐ ja
☐ nein

12. Haben Sie jemals mit Menschen, mit denen Sie zusammenleben, über Ihren Umgang mit Geld gestritten?

☐ ja
☐ nein

13. Wenn Sie Frage 12 mit "ja" beantwortet haben: War Streit um Geld jemals nachträglich auf Ihr Spielverhalten bezogen?

☐ ja
☐ nein

14. Haben Sie jemals von jemanden Geld geliehen und dieses aufgrund Ihres Spielens nicht zurückbezahlt?

☐ ja
☐ nein

15. Haben Sie jemals während Ihrer Arbeitszeit / während des Schulunterrichts gefehlt, um zu spielen?

☐ ja
☐ nein

16. Wenn Sie sich Geld geliehen haben zum Spielen oder für die Rückzahlung von Spielschulden, wo oder von wem liehen Sie es? (Überprüfen Sie bei jedem Mal, ob "ja" oder "nein")

a) vom Haushaltsgeld	☐ ja ☐ nein
b) vom Ehe-/Lebenspartner	☐ ja ☐ nein
c) von anderen Verwandten (auch angeheiratete)	☐ ja ☐ nein
d) von Banken oder Kreditinstituten	☐ ja ☐ nein
e) über Kreditkarten	☐ ja ☐ nein
f) von "Geldhaien"	☐ ja ☐ nein
g) vom Verkauf von Aktien, Wertpapieren oder anderen Anlagen	☐ ja ☐ nein
h) vom Verkauf von persönlichem oder familiärem Vermögen/Eigentum	☐ ja ☐ nein
i) durch Ausstellung ungedeckter Schecks	☐ ja ☐ nein
j) ich habe (hatte) einen Kredit bei einem Buchmacher	☐ ja ☐ nein
k) ich habe (hatte) einen Kredit bei einem Kasino	☐ ja ☐ nein

A 9 Personal data form (next 11 pages).

Angaben zur Person

1. Geschlecht:

   männlich..... O

   weiblich..... O

2. Alter:

   Bitte angeben: .....Jahre

3. Größe:

   Bitte angeben: .....m

4. Gewicht:

   Bitte angeben: .....kg

5. Familienstand:

   ledig..... O

   verheiratet / feste Partnerbeziehung..... O

   verwitwet..... O

   geschieden / getrennt..... O

6. Schulabschluß:

   a) Vor der letzten Hauptschluklasse abgeschlossen..... O

   b) Mit der letzten Hauptschlklasse abgeschlossen..... O

   c) Real-(Mittel-) oder Handelsschule ohne Abschlußprüfung..... O

   d) Real-(Mittel-) oder Handelsschule mit Abschlußprüfung..... O

   e) Gymnasium (Höhere Schule) ohne Abitur..... O

f) Abitur ohne anschließendes Studium..... ○

g) Abitur mit nicht abgeschlossenem Studium..... ○

h) Abitur mit abgeschlossenem Studium..... ○

7. Sind Sie zur Zeit berufstätig?

ja..... ○

oder sind Sie:

Schüler(in)/Student(in)..... ○

in Berufsausbildung..... ○

Rentner(in), Ruhestand..... ○

arbeitslos..... ○

8. Berufsgruppe:

Bitte den gegenwärtig bzw. zuletzt ausgeübten Beruf ankreuzen

Ungelernter Arbeiter (in)..... ○

Facharbeiter (in)..... ○

Angestellte (r) / Beamter im unteren Dienst..... ○

Angestellte (r) / Beamter im mittleren Dienst..... ○

Angestellte (r) / Beamter im höheren Dienst..... ○

Selbständige (r) (bis zu 9 Mitarbeiter)..... ○

Selbständige (r) (mehr als 10 Mitarbeiter)..... ○

Landwirt (in)..... ○

Freie Berufe..... ○

Keinen Beruf ausgeübt..... ○

9. Monatliches Nettoeinkommen

unter 1000 € ..... ○

1000 - 2000 € ..... ○

2000 - 3000 € ..... ○

3000 - 4000 € ..... ○

4000 - 5000 € ..... ○

5000 – 6000 € ..... ○

mehr als 6000 € ..... ○

Angaben zum Gesundheitszustand

1. Wie beurteilen Sie Ihren allgemeinen Gesundheitszustand?

Sehr gut..... ○
gut..... ○
schlecht..... ○
sehr schlecht..... ○

2. Leiden Sie unter Schlafstörungen?

ja..... ○ nein..... ○

3. Rauchen Sie?

ja..... ○ nein..... ○

Wenn ja, wieviel Zigaretten im Durchschnitt pro Tag?.....Stck.

4. Trinken Sie Alkohol?

Nie..... ○
1 mal pro Woche..... ○
2-3 mal pro Woche.... ○
4-5 mal pro Woche.... ○
täglich..... ○

5. Wieviel Tassen Kaffee/Tee nehmen Sie durchschnittlich am Tag zu sich?

Bitte angeben:.....

6. Nehmen Sie regelmäßig Medikamente ein?

ja..... O nein..... O

Wenn ja, welche und seit wann?

Bitte angeben:.....

7. Bestehen bei Ihnen Stoffwechselerkrankungen?

ja..... O nein..... O

Wenn ja, welche?

Bitte angeben:.....

8. Bestehen bei Ihnen Erkrankungen des Herz-/Kreislaufsystems (z. B. Bluthochdruck oder Angina Pectoris?)

ja..... O nein..... O

Wenn ja, welche?

Bitte angeben:.....

9. Bestehen bei Ihnen hormonelle Erkrankungen?

ja..... O nein..... O

Wenn ja, welche?

Bitte angeben:.....

10. Bestehen bei Ihnen Erkrankungen des Nervensystems/der Psyche (z. B. Depressionen)?

ja..... O nein..... O

Wenn ja, welche?

Bitte angeben:.....

11. Befinden Sie sich wegen psychischer Störungen in Behandlung?

ja..... O nein..... O

Wenn ja, wegen welcher und seit wann?

Bitte angeben:.....

12. Bestehen bei Ihnen chronische Erkrankungen?

ja..... O nein..... O

Wenn ja, welche?

Bitte angeben:.....

Glücksspiel

Datum: ..... **Vp.-Nummer: .....**

a) Wie **aufgeregt/angespannt** haben Sie sich **während** des Glücksspiels gefühlt? Nennen Sie mir bitte das Ausmaß der Aufregung/Anspannung anhand der vorliegenden Skala (von gar nicht bis sehr stark).

gar nicht	schwach	etwas	mittelmäßig	ziemlich	stark	sehr stark
O	O	O	O	O	O	O

b) Wie **froh/vergnügt** haben Sie sich **während** des Glücksspiels gefühlt? Nennen Sie mir bitte das Ausmaß der Freude/des Vergnügens anhand der vorliegenden Skala (von gar nicht bis sehr stark).

gar nicht	schwach	etwas	mittelmäßig	ziemlich	stark	sehr stark
O	O	O	O	O	O	O

c) Wie **zufrieden/wohl** haben Sie sich **während** des Glücksspiels gefühlt? Nennen Sie mir bitte das Ausmaß der Zufriedenheit/des Wohlgefühls anhand der vorliegenden Skala (von gar nicht bis sehr stark).

gar nicht	schwach	etwas	mittelmäßig	ziemlich	stark	sehr stark
O	O	O	O	O	O	O

d) Wie enttäuscht/ niedergeschlagen haben Sie sich **während** des Glücksspiels gefühlt? Nennen Sie mir bitte das Ausmaß der Enttäuschung anhand der vorliegenden Skala (von gar nicht bis sehr stark).

gar nicht	schwach	etwas	mittelmäßig	ziemlich	stark	sehr stark
O	O	O	O	O	O	O

e) Wie ausgeprägt ist im Moment Ihre **Lust zum Spiel/Ihr Verlangen nach einer Fortsetzung des Spiels**?

gar nicht	schwach	etwas	mittelmäßig	ziemlich	stark	sehr stark
O	O	O	O	O	O	O

Angaben zum Spiel

Vp.-Nr. .....

1) Bitte geben Sie an, in welchem Ausmaß Sie sich gefühlsmäßig auf das Spiel eingelassen haben.

gar nicht	schwach	etwas	mittelmäßig	ziemlich	stark	sehr stark
O	O	O	O	O	O	O

2) Vergleichen Sie bitte das heutige Ausmaß Ihrer emotionalen Beteiligung am Spiel mit dem Ausmaß bei vorangegangenen Spielbankbesuchen/Glücksspielen im Internet
Das Ausmaß der emotionalen Beteiligung am Spiel war heute im Vergleich

viel schwächer	schwächer	gleich	stärker	viel stärker
O	O	O	O	O

Wie häufig haben Sie in den letzten 12 Monaten im Durchschnitt an folgenden Glücksspielen teilgenommen bzw. nicht teilgenommen? Geben Sie bitte für jedes Glücksspiel an, ob Sie sich **gar nicht, weniger als 1 mal im Monat, bis zu 3 mal im Monat, 1- bis 3 mal pro Woche** oder **mehr als 3 mal pro Woche** daran beteiligt haben.

	gar nicht teilge-nommen	weniger als 1 mal im Monat	bis zu 3 mal im Monat	1 bis 3 mal pro Woche	mehr als 3 mal pro Woche
Lotto/Toto/Rennquintett/Spiel 77.....	O	O	O	O	O
Oddset.....	O	O	O	O	O
Rubbellotto.....	O	O	O	O	O
Fernsehlotterien.....	O	O	O	O	O
Klassenlotterien.....	O	O	O	O	O
PS-Sparen und Gewinnsparen.....	O	O	O	O	O
Pferdewetten.....	O	O	O	O	O
Roulette.....	O	O	O	O	O
Black Jack.....	O	O	O	O	O
Baccara.....	O	O	O	O	O
Glücksspielautomaten in Spielcasinos.	O	O	O	O	O
Geldspielautomaten in Spielhallen und Gaststätten.....	O	O	O	O	O
Fungame-Automaten in Spielhallen und Gaststätten.....	O	O	O	O	O
Glücksspiele in Hinterzimmern von Gaststätten oder in privaten Runden (Karten-, Würfelspiele usw. um Geld)	O	O	O	O	O
Börsenspekulationen.....	O	O	O	O	O
Poker und andere Glücksspiele im Internet.....	O	O	O	O	O

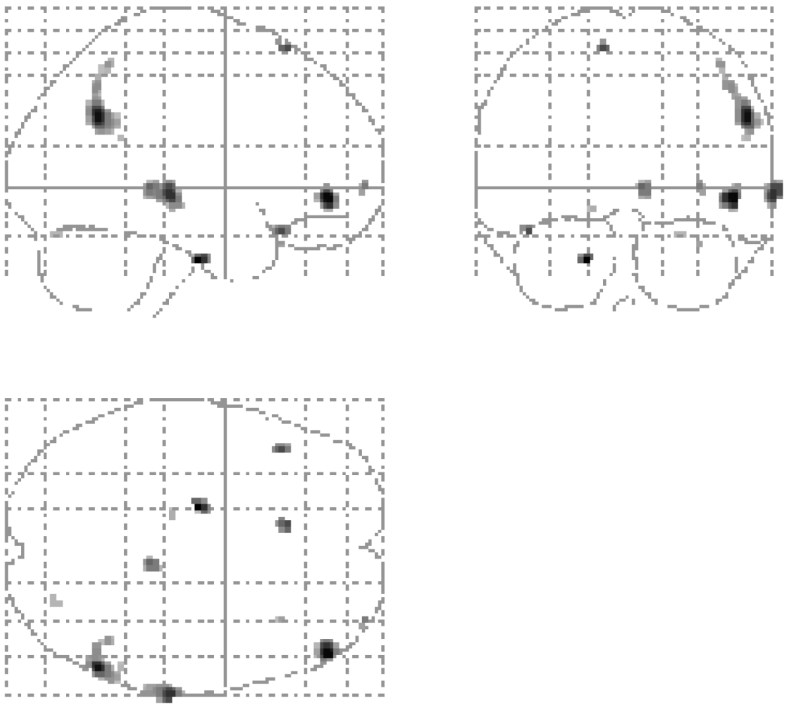
Denken Sie noch einmal an die letzten 12 Monate. Bitte versuchen Sie zu schätzen, wie viel Euro pro Monat Sie durchschnittlich bei den folgenden Wetten bzw. den folgenden Glücksspielen eingesetzt/verloren haben.

☞ *Bitte geben Sie die Beträge auf ganze Euro gerundet an!*

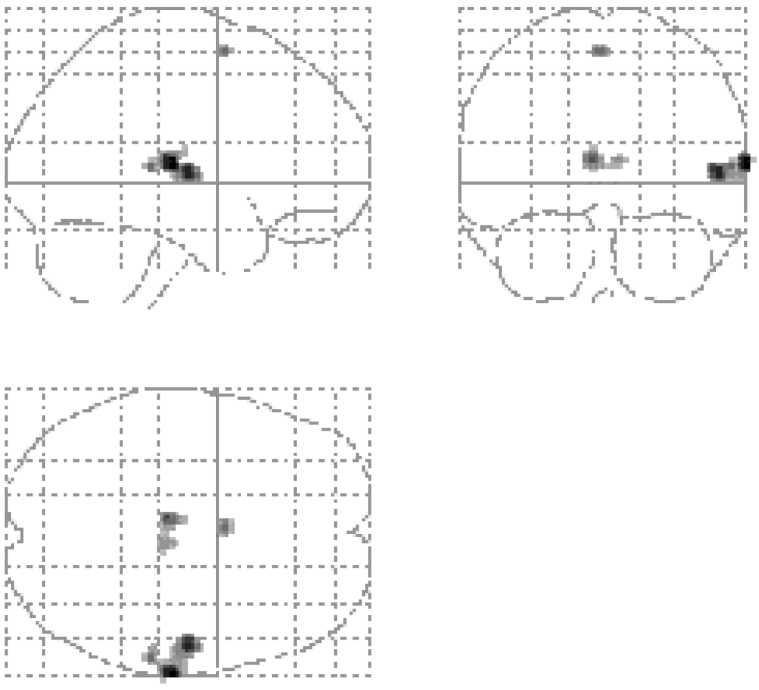
	durchschnittlich eingesetzt pro Monat in Euro
Fernsehlotterie	
Klassenlotterie	
Lotto/Toto/Keno	
Quicky (Lottoautomaten, Internet)	
Sportwetten in Annahmestellen (Oddset)	
Sportwetten im Internet (Oddset und andere)	
Pferdewetten	

	durchschnittlich verloren pro Monat in Euro
Geldspielautomaten („Daddelautomaten") in Spielhallen, Gaststätten, Imbissstuben	
Roulette, Black Jack, Poker etc. im Spielcasino (großes Spiel)	
Automatenspiel im Spielcasino (kleines Spiel)	
Roulette/Automatenspiel im Internet (Internetspielcasino)	
Poker und andere Glücksspiele im Internet.	
Karten- u. Würfelspiele in Hinterzimmern	

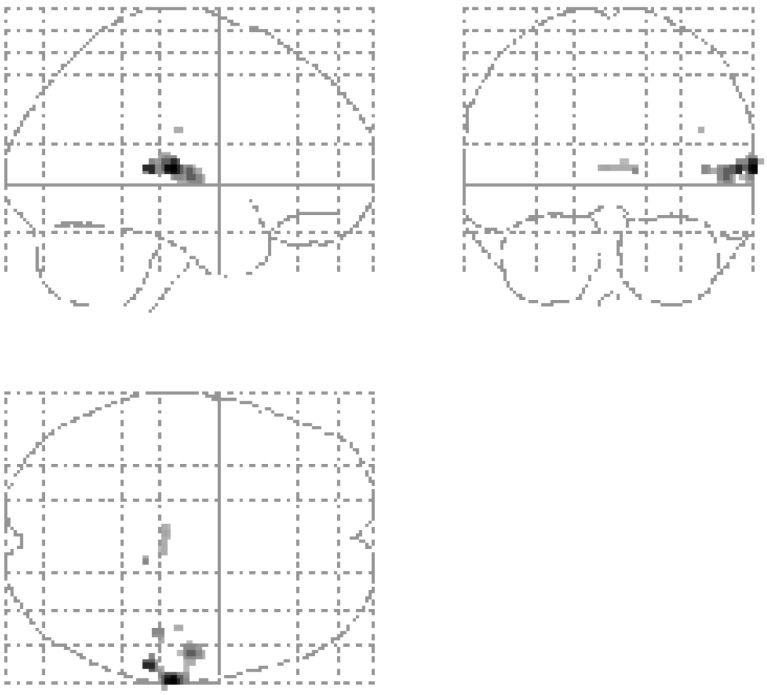
A 10 Glass brains showing the activation pattern of the high-risk vs. low-risk contrast in PG during experiment 1 (p<.001 uncorrected; see also Table 2.1 A).



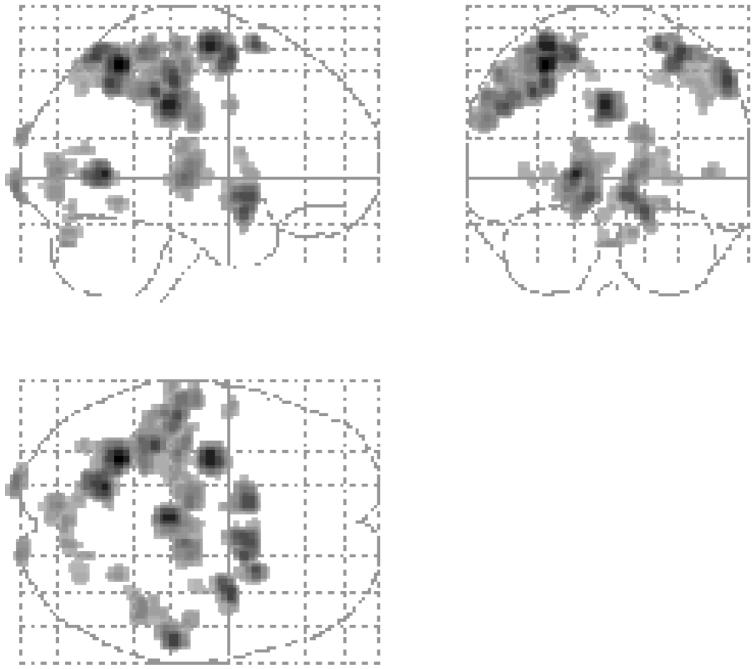
A 11 Glass brains showing the activation pattern of the low-risk vs. high-risk contrast in OG during experiment 1 (p<.001 uncorrected; see also Table 2.1 C).



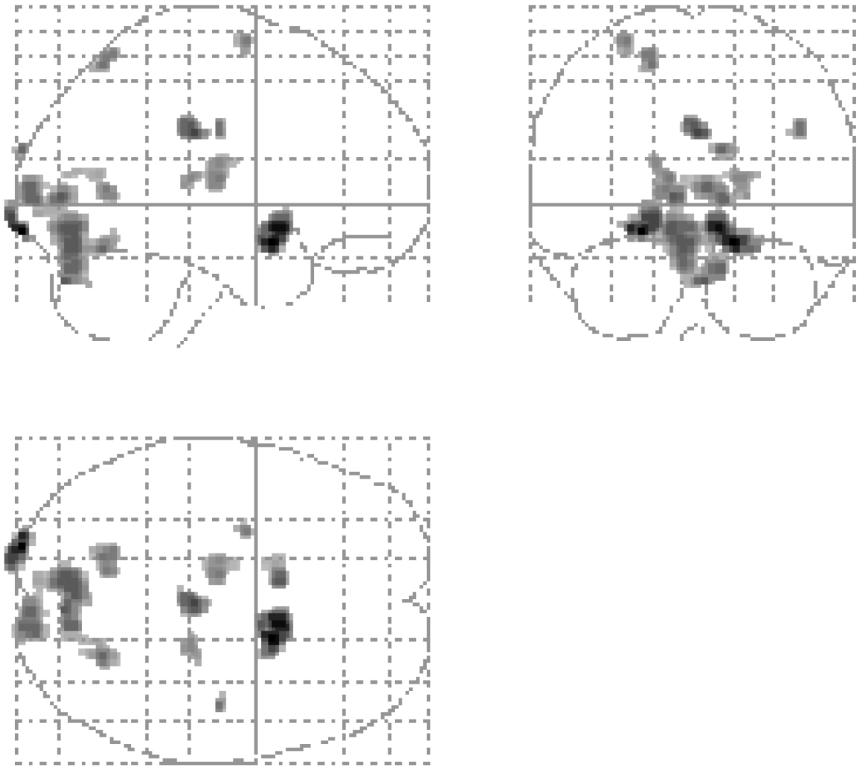
A 12 Glass brains showing the activation pattern of the low-risk vs. high-risk interaction contrast in OG vs. PG during experiment 1 (p<.001 uncorrected; see also Table 2.2 B).



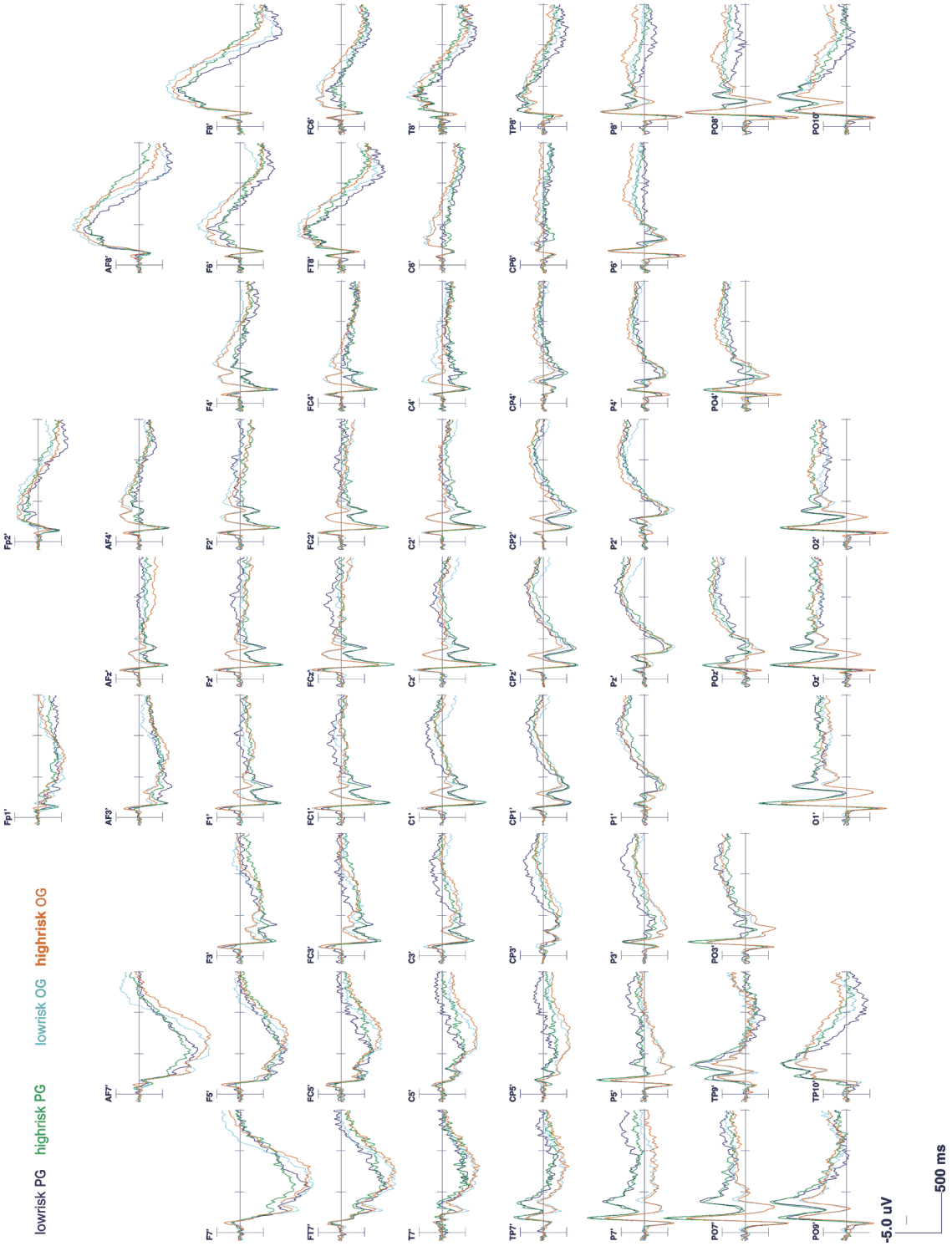
A 13 Glass brains showing the activation pattern of the win vs. lose contrast in PG during experiment 1 (p<.05 FWE corrected; see also Table 2.3 A).



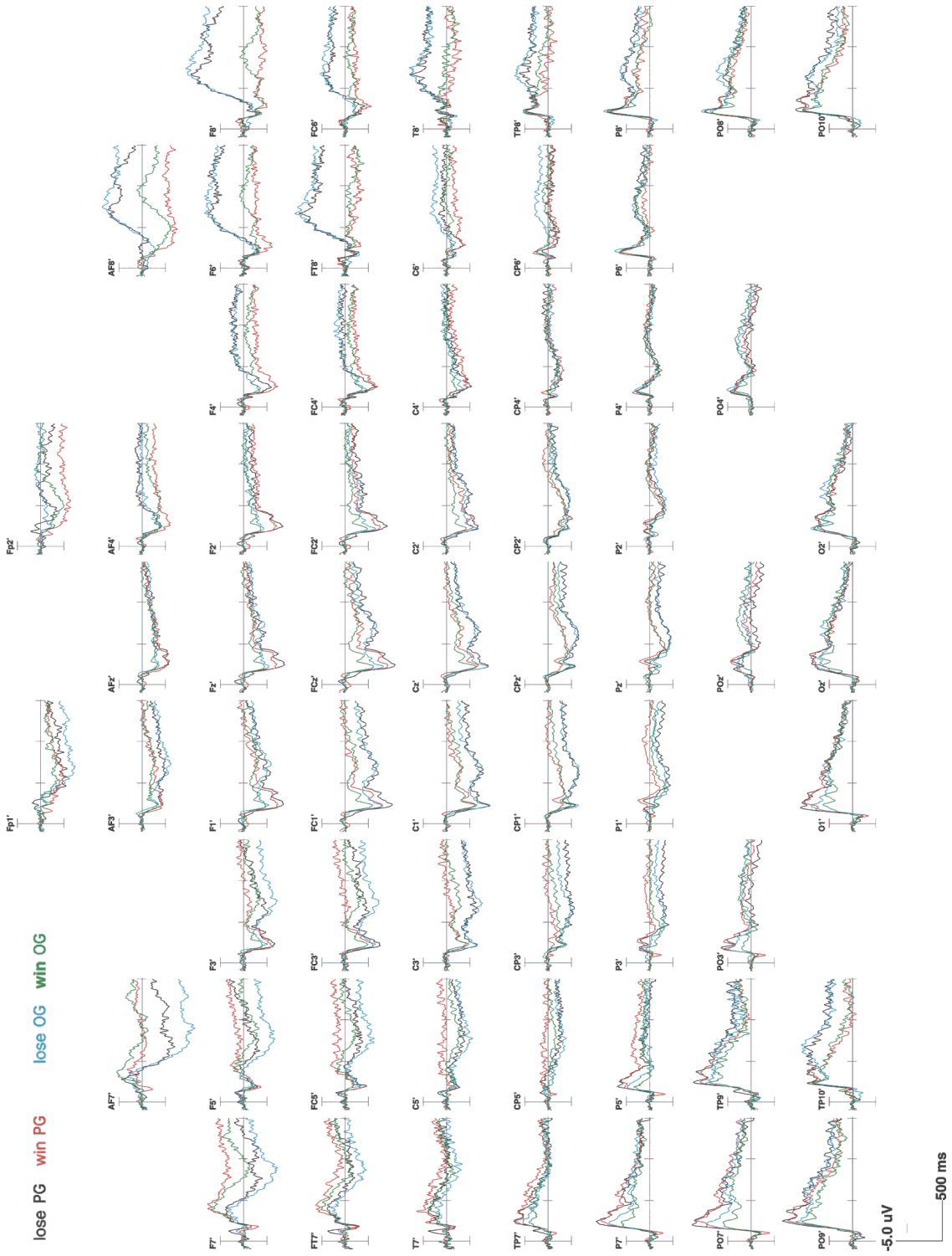
A 14 Glass brains showing the activation pattern of the win vs. lose contrast in OG during experiment 1 (p<.05 FWE corrected; see also Table 2.3 B).



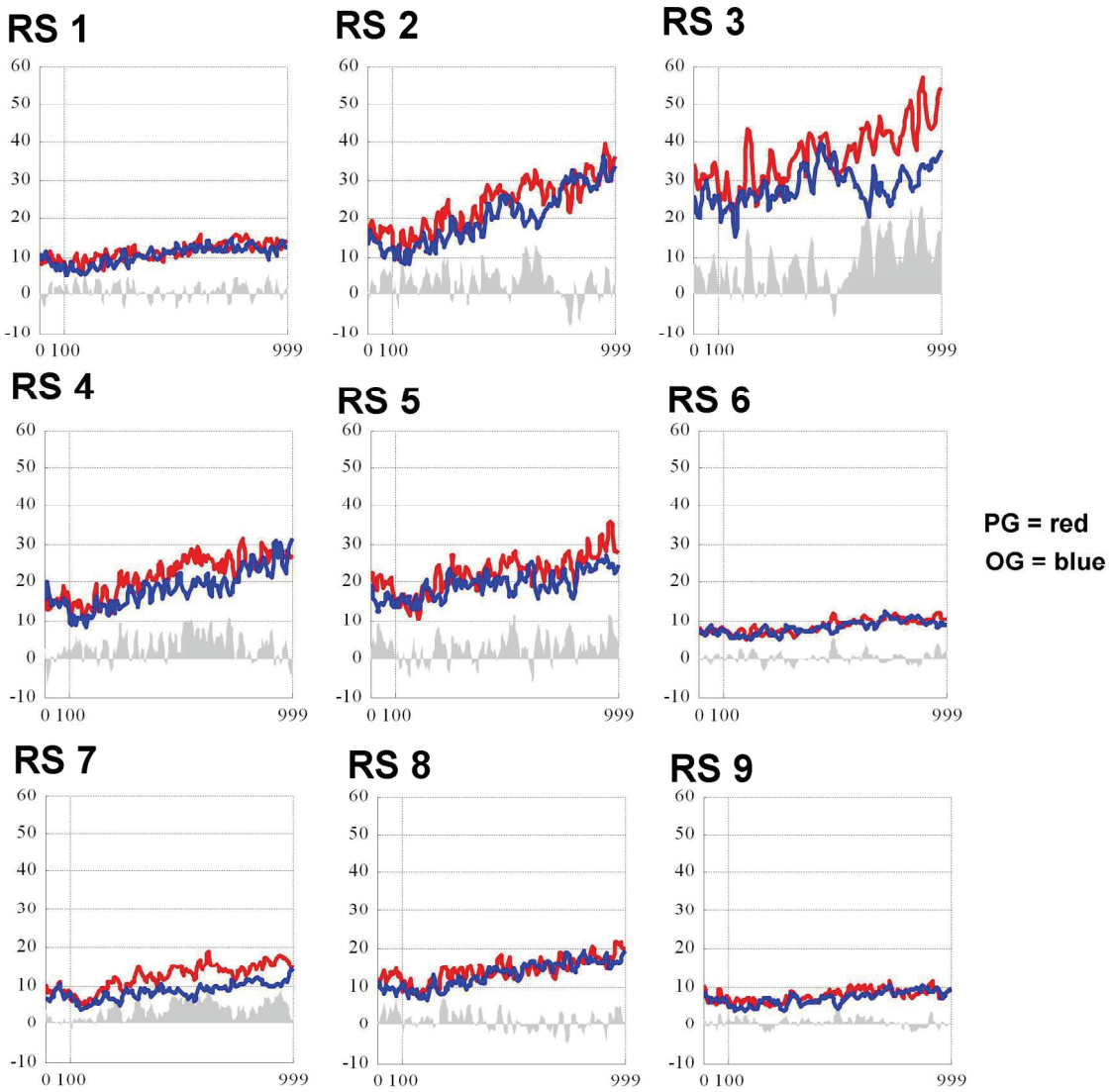
A 15 ERPs of the 64 electrode positions for the start of the game (low-risk PG: dark blue; high-risk PG: green; low-risk OG: light blue; high-risk OG: orange).



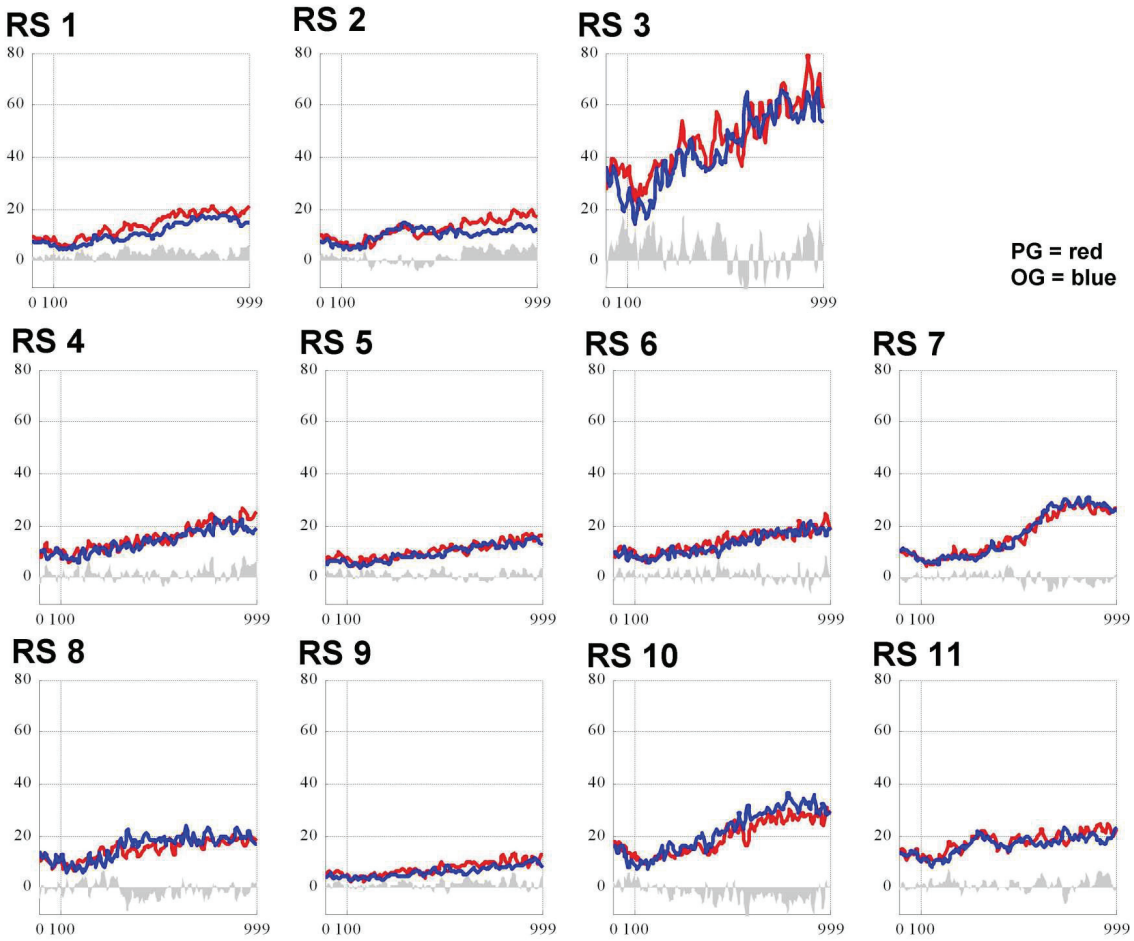
A 16 ERPs of the 64 electrode positions for the end of the game (lose PG: black; win PG: red; lose OG: light blue; win OG: green).



A 17 Source waveforms (y-axis = RMS, root mean square) for PG (red line) and OG (blue line) between 0-999 ms (x-axis) for the start of the game. Gray shaded areas indicate difference waves of source waveforms between PG and OG. The regional source (RS) numbers represent brain regions listed in Figure 3.7.



A 18 Source waveforms (y-axis = RMS, root mean square) of PG (red line) and OG (blue line) over the 0-999 ms time window (x-axis) for the end of the game. Gray shades show difference waves of source waveforms between PG and OG. The regional source (RS) numbers represent brain regions shown in Figure 3.9.



T 1 Statistics of the fMRI constrained source model for the start of the game to test for main effects of group or the GROUP x regional source (RS) interaction for twenty 50 ms time windows between 0 and 1000 ms (n.s. = not significant; GG = Greenhouse-Geisser corrected; see also upper part of Figure 3.8).

time window (ms)	factor	df	F	p	GG
0-50	group x RS	3.25	1.79	.081	0.152
0-50	group	1	1.78	n.s.	
50-100	group x RS	4.14	1.17	n.s	n.s
50-100	group	1	3.13	.091	
100-150	group x RS	2.17	0.69	n.s.	n.s.
100-150	group	1	1.67	n.s.	
150-200	group x RS	2.43	0.23	n.s.	n.s.
150-200	group	1	1.1	n.s.	
200-250	group x RS	2.15	1.55	n.s.	n.s.
200-250	group	1	2.58	n.s.	
250-300	group x RS	4.17	1.37	n.s.	n.s.
250-300	group	1	3.13	.091	
300-350	group x RS	4.07	0.71	n.s.	n.s.
300-350	group	1	3.95	.059	
350-400	group x RS	3.84	0.867	n.s.	n.s.
350-400	group	1	3.2	.087	
400-450	group x RS	3.37	0.97	n.s	n.s
400-450	group	1	1.32	n.s	
450-500	group x RS	3.39	0.81	n.s	n.s
450-500	group	1	2.26	n.s	
500-550	group x RS	3.3	0.5	n.s	n.s
500-550	group	1	2.38	n.s	
550-600	group x RS	3.97	2.12	.037	0.086
550-600	group	1	2.24	n.s.	
600-650	group x RS	3.71	1.33	n.s.	n.s.
600-650	group	1	3.01	.097	
650-700	group x RS	3.28	2.58	.011	0.055
650-700	group	1	4.67	.042	
700-750	group x RS	4.54	2.53	.012	0.038
700-750	group	1	3.02	.096	
750-800	group x RS	3.62	2.92	.004	0.03
750-800	group	1	1.98	n.s.	
800-850	group x RS	3.73	1.33	n.s.	n.s.
800-850	group	1	0.48	n.s.	
850-900	group x RS	4.18	2.06	.042	0.089
850-900	group	1	1.28	n.s.	
900-950	group x RS	4.04	1.7	n.s.	n.s.
900-950	group	1	3	.097	
950-1000	group x RS	3.28	0.87	n.s.	n.s.
950-1000	group	1	1.93	n.s.	

T 2 Statistics based on a fMRI constrained source model for the end of the game to test for main effects of GROUP or the GROUP x regional source (RS) interaction for twenty 50 ms time windows between 0 and 1000 ms (n.s. = not significant; GG = Greenhouse-Geisser corrected see also lower part of Figure 3.8). *The GROUP x RS interaction in the 400-450 ms time window was calculated with the 8 active RS (RS 3-5 were switched off at this time).

time window (ms)	factor	df	F	p	GG
0-50	group x RS	2.48	0.26	n.s.	n.s.
0-50	RS	1	0.46	n.s.	
50-100	group x RS	3.23	3.7	.001	0.014
50-100	RS	1	4.38	.048	
100-150	group x RS	3.36	2.06	.029	n.s.
100-150	RS	1	1.16	n.s.	
150-200	group x RS	3.36	2.34	.012	0.074
150-200	RS	1	2.57	n.s.	
200-250	group x RS	2.88	1.87	.051	n.s.
200-250	RS	1	2.86	n.s.	
250-300	group x RS	3.4	0.6	n.s	n.s
250-300	RS	1	0.7	n.s	n.s
300-350	group x RS	2.26	0.29	n.s	n.s
300-350	RS	1	0.41	n.s	n.s
350-400	group x RS	2.16	0.34	n.s	n.s
350-400	RS	1	0.48	n.s	n.s
400-450	group x RS	4.31	1.94	.066*	n.s
400-450	RS	1	0.01	n.s.	
450-500	group x RS	3.16	0.99	n.s.	n.s.
450-500	RS	1	0	n.s.	n.s.
500-550	group x RS	2.2	1.12	n.s.	n.s.
500-550	RS	1	1.29	n.s.	n.s.
550-600	group x RS	2.4	0.31	n.s.	n.s.
550-600	RS	1	0	n.s.	n.s.
600-650	group x RS	2	0.7	n.s.	n.s.
600-650	RS	1	0.08	n.s.	n.s.
650-700	group x RS	2	0.25	n.s.	n.s.
650-700	RS	1	0.11	n.s.	n.s.
700-750	group x RS	2.53	0.25	n.s.	n.s.
700-750	RS	1	0.04	n.s.	n.s.
750-800	group x RS	3.03	0.41	n.s.	n.s.
750-800	RS	1	0.01	n.s.	n.s.
800-850	group x RS	2.64	0.3	n.s.	n.s.
800-850	RS	1	0.01	n.s.	n.s.
850-900	group x RS	3.9	0.34	n.s.	n.s.
850-900	RS	1	0.21	n.s.	n.s.
900-950	group x RS	3.71	0.68	n.s.	n.s.
900-950	RS	1	0.61	n.s.	n.s.
950-1000	group x RS	3.82	0.31	n.s.	n.s.
950-1000	RS	1	1.26	n.s.	n.s.

T 3 Means and standard deviations (SD) of the regional source (RS) moments (root mean square = RMS) only for significant or trend to significant time windows during the start of the game for PG and OG (see T 1). The RS numbers represent brain regions listed in Figure 3.7.

start of the game			
time window (ms)	RS	OG Mean (±SD)	PG Mean (±SD)
0-50	5	15 (±4.53)	20.8 (±5.45)
0-50	8	9.64 (±2.43)	12.4 (±3.79)
50-100	2	11.42 (±4.65)	17.11 (±7.7)
50-100	8	9.23 (±3.46)	13.14 (±4.25)
250-300	7	6.32 (±1.83)	11.22 (±4.62)
250-300	8	9.25 (±3.35)	13.59 (±4.93)
350-400	7	7.82 (±2.76)	12.99 (±4.45)
550-600	4	17.75 (±7.24)	26.65 (±12.9)
550-600	5	18.33 (±7.86)	26.03 (±9.17)
550-600	7	7.27 (±4.13)	13.48 (±4.93)
600-650	2	20.89 (±7.85)	28.51 (±9.53)
600-650	4	19.81 (±7.87)	26.44 (±9.97)
600-650	7	8.53 (±3.75)	14.65 (±5.88)
650-700	2	19.73 (±8.04)	29.64 (±13.19)
650-700	3	26.44 (±8.58)	40.39 (±19.12)
650-700	4	19.63 (±5.67)	25.62 (±9.68)
650-700	7	9.2 (±3.78)	16.11 (±6.63)
700-750	3	27.04 (±10.03)	41.2 (±14.95)
700-750	4	18.84 (±7.04)	25.13 (±7.71)
700-750	7	9.38 (±1.86)	13.78 (±6.59)
750-800	3	26.34 (±9.06)	43.18 (±18.4)
850-900	3	29.76 (±9.7)	46.08 (±18.54)
850-900	7	11.11 (±4.06)	16.07 (±8.58)
900-950	3	32.51 (±12.08)	49.96 (±20.33)
900-950	7	9.86 (±3.55)	16.6 (±9.05)

T 4 Means and standard deviations (SD) of the regional source (RS) moments (root mean square = RMS) only for significant or trend to significant time windows during the end of the game for PG and OG (see T 2). The RS numbers represent brain regions listed in Figure 3.9.

end of the game			
time window (ms)	RS	OG Mean (±SD)	PG Mean (±SD)
50-100	2	6.13 (±2.23)	7.71 (±2.14)
50-100	3	22.74 (±10.84)	34.58 (±10.59)
100-150	3	20.94 (±9.29)	28.01 (±8.63)
150-200	3	19.81 (±7.46)	27.93 (±10.49)
150-200	5	4.48 (±1.72)	6.12 (±2.7)
200-250	1	5.83 (±2.73)	9.13 (±3.58)
400-450	1	8.13 (±2.26)	13.21 (±4.48)