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Pathological gambling is linked to reduced activation of the mesolimbic reward system

Dissertation

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1. Summary

By analogy to drug dependence, pathological gambling may relate to a dysfunctional cerebral reward system. Studying pathological gamblers and controls during a guessing game using functional magnetic resonance imaging (fMRI), we observed changes in cerebral dopaminergic regions in pathological gamblers. Results correlated with gambling severity, linking dysfunction of these areas to clinical symptoms.

2. Introduction

2.1 Structure of the mammal reward system

Systems of reinforcement and goal-directed behaviour exist more or less in all living structures. From chemotaxis to choosing stock options at the NASDAQ™ stock exchange, goal directed behaviour is essential in living organisms. Reward establishes value systems and serves as references for behavioural decisions. A specialised neural network appears to manage reward processing. This so called reward system projects throughout the Midbrain, the Basal Ganglia, Limbic and Frontal areas and can be subdivided into numerous anatomical, biochemical and behavioural aspects. It is involved from basic instincts like eating and sexuality to highly complex social aspects.

Dopaminergic projections from the Ventral Tegmental Area (VTA) to the Striatum, Anterior Cingulate Cortex (ACC), the Amygdale and Hippocampus and Prefrontal structures form a Midbrain-Extrapyramidal-Forebrain circuit of reward processing (Koob, 1992). Within this circuitry, the Ventral Striatum and its Nucleus Accumbens play a central role (Vaccarino, 1985). It is well connected to Prefrontal and Frontal cortices, including the Orbitofrontal Cortex (OFC) (Schoenbaum, 2003). Limbic structures like the Anterior Cingulate Cortex (ACC), the Amygdala and Hippocampus are also involved in reward processing and show high connectivity to other reward related areas (Aggleton, 1981). In perspective of reward related goal-directed behaviour and conditioning, the Pedunculopontine Tegmental Nucleus (PTN), Medial-Dorsal Nuclei of Thalamus (MDN) and Premotor areas play a central role (Inglis, 1994). Along the structural dissociation, the reward process itself can be dissected into different aspects such as anticipation, salience, arousal and experience of reward. Reward-related issues like decision making, impulse control, goal directed behaviour and learning are embedded in the reward system and cannot be seen isolated from reward processing.

Reward processing has been studied extensively in mammals, especially mice, rats and primates, finding striking anatomical and neurochemical parallels to human reward processing. Because of this, we will have an extensive view on reward processing in mammals in this thesis.

Research with "reward-gene"-knock-out animals, placed lesions and invasive real-time procedures (electric stimulation, micro-dialysis, voltammetry and single neurone analysis) in combination with behavioural experiments enabled a detailed analysis of reward processing (Becker 1999, Burgdorf 2000, Cardinal 2005, Carelli 1994, 2003, Gifford 2000, McAlonan 1993, Nicola 2004, Olds 1969, Pears 2003, Pecina 2000, Pothuizen 2005, Schmelzeis 1996, Shidara 2002, Xi 1998). Drug effects and addiction models in mammals also appear to be comparative to humans and can help in understanding addiction models.

2.1.1 Ventral Striatum

The Ventral Striatum and its dopaminergic projections from the VTA have been found to play a central role throughout various species in reinforcement, reward processing and learning (Carelli 1993, Everitt 1999, Jackson 2001, Jones 1992, Olds 1969, Panagis 1997, Setlow 2003). The Ventral Striatum itself can be divided into telencephalic components like the Caudate Nucleus, the Ventral Putamen, shell and core of the Nucleus accumbens and the diencephalic Ventral Pallidum. Due to the central role in this study, the Nucleus Accumbens is described in its own chapter.

In primates, up to 80% of all dopamine neurones from the Medial Tegmental Area projecting to the Nucleus Accumbens and Frontal regions show phasic activation when liquid or solid rewards or stimuli that predict them are given (Ljungberg, 1992). Apicella showed responding neurones in monkeys to a delivery of liquid reward in the Dorsal and Ventromedial parts of the anterior Putamen, in the Dorsal and Ventral Caudate, and in the Nucleus Accumbens (Apicella, 1991).

The Ventral Striatum of rats processes information acquired through associative learning. Striate neurons fire selectively to odour cues predictive of either appetitive or aversive outcomes. Few neurons were selective when first exposed to the odours, but many acquired this differential activity as rats learned the significance of the cues. A

substantial proportion of these neurones encoded the cues` learned motivational significance, and these neurones tended to reverse their firing selectivity after reversal of odour-outcome contingencies. Other neurones that became selectively activated during learning did not reverse, but instead appeared to encode specific combinations of cues and associated motor responses. The results support a role for the Ventral Striatum in using the learned significance, both appetitive and aversive and of predictive cues to guide behaviour (Setlow, 2003). In monkeys trained in a classical conditioning task, the effects of striate dopamine depletion have been tested. Unilateral dopamine loss substantially reduced the acquired sensory responsiveness of striate neurones monitored electrophysiologically. This effect was ipsilateral and selective. This suggests that the nigro-striate system modulates expression of neuronal response plasticity in the Striatum during sensorimotor learning (Aosaki, 1994).

2.1.2 Nucleus accumbens (Nacc)

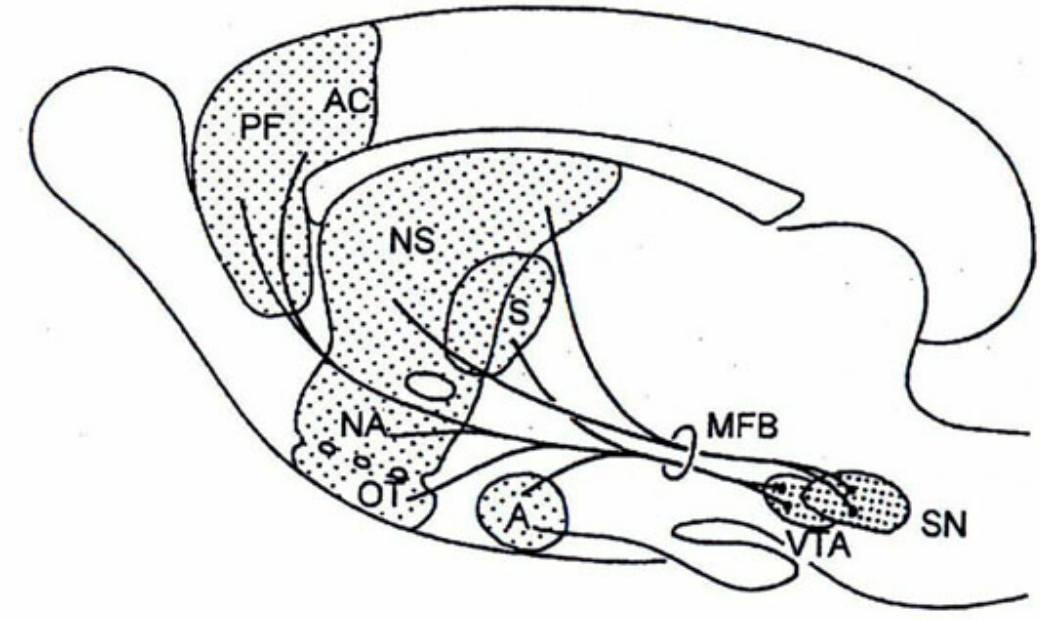


Fig. 1: Scheme of the dopaminergic mesotelenzephalen system in a rat (PF:präfrontaler Kortex; AC: vorderer cingulärer Kortex; NS: Striatum; S: Septum; NA: Nucleus accumbens; OT: Tuberculum olfactorium; A: amygdala; MFB: medial Vorderhirnbündel; VTA: ventral tegmental area; SN: Substantia nigra); (Dunnett and Robbins, 1992)

The Nacc is part of the Ventral Striatum and can be divided into core and shell including various specialised neurons. In the last years the role of the Nacc has been

discovered in more specific ways than plain detection of reward – such aspects as modelling differences of anticipation and outcome regarding reward magnitude and availability, modelled in the prediction-error (Schultz, 2000), (Yacubian, 2006) and related processes such as limbic-motor interfacing, reward-delay-management and food regulation to name a few (Roitmann 2004, Jones 1992, Inglis 1994).

Behavioural aspects

Blocking dopamine D1 and D2-receptors in shell and core of the Nacc altered feeding and motor behaviour in rats. It suppressed spontaneous motor activity and shifted the structure of feeding towards longer duration, but did not alter the total amount of food consumed. In the shell, the effects of D1 receptor blockade tended to be of greater magnitude than the effects of D2 receptor blockade, although major differences between core and shell effects were not observed (Baldo, 2002).

Cues that signal for an opportunity to respond for sucrose evoked dopamine-release in the Nacc of rats. This reflects a learned association between the cues and sucrose availability. Lever presses for sucrose occurred at the peak of the dopamine surges. After lever presses and while sucrose was delivered and consumed, no further increases in dopamine were detected. Rather, dopamine returned to baseline levels. This suggests subsecond dopamine signalling in the Nacc as a real-time modulator of food-seeking behaviour (Roitman, 2004). The Nacc regulates “delay”-problems in reward related learning. The delay-problem means that small immediate reward must be of lower preference than delayed big rewards for productive instrumental learning. To analyse this, rats with excitotoxic or sham lesions of the Nacc core acquired an instrumental response with different delays between the lever-press response and reinforcer delivery. Core lesions did not hinder learning in the absence of delays, but the Nacc core-lesioned rats were impaired in learning when there was a delay, relative to sham-operated controls. This shows the importance of the Nacc in regulating the magnitude and delay of receiving of reward, thus being essential in instrumental learning (Cardinal, 2005). Reward-delay management, controlled by accumbal dopamine may be important for enabling rats to overcome behavioural constraints, such as work-related response costs, and may be critical for the behavioural organisation and conditioning processes that enable animals to engage in vigorous responses, such as barrier climbing, or to emit

large numbers of responses in ratio schedules in the absence of primary reinforcement (Salamone, 2003).

The shell and core of Nacc is often called the limbic–motor interface, connecting reward and motivation to goal-directed behaviour. Accumbal dopamine is thought to be involved in responsiveness to conditioned stimuli and activational aspects of motivation (Salamone, 2003). Nicola found firing of subpopulations of the Nacc neurones to encode both the predictive value of environmental stimuli and the specific motor behaviours required to respond to them (Nicola, 2004). In rats, Nacc lesions influenced locomotor activity in a complex pattern. Two separate groups of Nacc - lesioned rats with either large (NACT = 90% Nacc dopamine depletion) or partial (NACP = 67% Nacc dopamine depletion) lesions were compared. NACT rats were spontaneously hypoactive whereas NACP rats were hyperactive compared with sham-operated controls in a food deprived situation. The Nacc lesion did not keep rats from learning conditioned behaviour. When food supplements were paired with the light signals, all subjects developed a conditioned locomotor response. During the first few days of conditioning, the response to this conditioning procedure was markedly greater in the NACP group, whereas the response in the NACT group was unaffected initially and actually enhanced during the latter days of testing. All Nacc lesions attenuated the locomotor response to amphetamine, and the NACT group showed a supersensitive response to apomorphine. Here, the Nacc is involved in spontaneous, conditioned, and drug-induced locomotor activity. Further it seems that dopaminergic mechanisms of the Nacc control the magnitude of the behavioural response to incentive stimuli (Jones, 1992).

Another study showed Nacc (shell and core) - lesioned monkeys with an increase in activity and aggressive behaviour in response to stress. In addition, the Nucleus Accumbens - lesioned monkeys performed normally during a button press acquisition task, but extinguished faster on a button press extinction task than the control monkeys (Stern, 1996). Administration of cocaine (a reuptake inhibitor for dopamine, noradrenalin and serotonin) resulted in a dose dependent stimulation of locomotor activity and changes in dopamine transmission in the Nacc shell and core, the Dorsal Caudate, and the Medial PFC. From the Nacc signals are relayed forward through the Dorsomedial Nucleus of the Thalamus to the Medial PFC, but the other major pathway

from this site is a descending innervation to the PTN. Information carried by these descending neurones has been linked with both the output of locomotor activity and incentive-related information. Locomotor activity was compared to the acquisition of responding with conditioned reinforcement in rats with PTN-lesions after injections of amphetamine directly into the Nacc. In this experiment, rats were introduced to a rewarding lever and a non-rewarding lever. Lesions of the PTN did not alter locomotion stimulated directly from the Nacc in rats. However, differences appeared in the conditioned reinforcement paradigm. The rats directed their attention almost entirely towards pressing the levers, but did not appear to be able to discriminate between them, while controls focused almost all their efforts on pressing the reinforcing lever. These results indicate PTN-lesions to disrupt an element of reward-related responding, but do not affect the production of locomotor activity. This implicates the PNT to be in the formation of stimulus-reward associations (Inglis, 1994). Comparing core vs. shell lesioned rats gives evidence for a functional separation of core and shell regarding motor-control. Core inactivation resulted in akinesia directly after infusion, but in hyperactivity 24 and 72 h thereafter in contrast to the control group. The persistent hyperactivity could be explained by compensatory mechanisms in the Nucleus Accumbens. Interestingly, inactivation of the shell was ineffective (Pothuizen, 2005).

Goal directed behaviour seems to be controlled by a triadic relationship of the Nacc, the Amygdala and the PFC. The PFC has an inhibitory control on accumbal dopamine release during Amygdala activation. In freely moving rats, microstimulation of the basolateral Amygdala (at intensities that produced mild behavioural activation) produced an increase in glutamate efflux in the PFC and the Nucleus Accumbens shell. During the stimulation, dopamine release increased only in the PFC, but not in the Nacc. An increase in accumbal dopamine release was observed during the stimulation if glutamate activation in the PFC was inhibited at either presynaptic or postsynaptic levels. Some behaviours expressed during the stimulation were intensified in animals in which the PFC glutamate activation was blocked. In addition, these animals continued to express stimulus-induced behaviours after the termination of stimulation, whereas normal poststimulus behaviours such grooming were not displayed as frequently. This suggests that the PFC influences the behavioural impact of the Amygdala activation via a concomitant active suppression of accumbal dopamine release. Absence of this cortical influence appears to result in an aberrant pattern of behavioural expression in

response to Amygdala activation, including behavioural perseveration after stimulus termination (Jackson, 2001).

Specification of Nacc - neurons

In cocaine self-administration and water reinforcement sessions, Nacc neurons showed dissociable responses. In an experiment with rats, cocaine self-administration was enabled with a response on a lever. Nacc neurons could be sub-grouped in respect to different phases of reaction and to different nature of rewards. Nucleus accumbens neurones exhibited distinct patterns of phasic activity relative to the reinforced response. Three of these firing patterns were observed during both cocaine self-administration and water reinforcement sessions. Response-related activity was categorised by (i.) cells that showed an anticipatory increase in firing rate during the pre-response phase (type anticipatory neurone = PR), and by (ii.) cells that were excited (type response activated = RFE) or (iii.) inhibited (type response inhibition = RFI) following the response. PR and RFE cells showed significantly *reduced* peak firing during cocaine self-administration, compared to similar cells in water reinforcement sessions. A fourth type of Nacc firing pattern was observed only in cells recorded during cocaine self-administration sessions. PR and RF neurones exhibited two distinct peaks, one preceding the response and terminating at response completion, and a second peak immediately following the response with an inhibitory period between the two peaks (Carelli, 1993, 1994, 2003). Another study of Nacc cells displayed patterned discharges relative to the cocaine-reinforced response, or relative to the water or food-reinforced response, but not both, indicating cocaine activates a neural circuit that is largely separate from the circuit that processes information about food and water reward. This functional organisation was proven not to be a direct consequence of chronic drug exposure (Carelli, 2000).

Gender differences

There are distinct gender differences in the Nacc. In female rats the gonadal hormones estrogen and progesterone modulate dopamine activity in the Striatum and the Nacc. There is an estrous cycle-dependent variation in basal extracellular concentration of striate dopamine, in amphetamine stimulated dopamine release and in striate dopamine mediated behaviours. Ovariectomy decreases these dopamine concentration variations. Also, estrogen rapidly and directly acts on the Striatum and the Nacc, via a G-protein-

coupled external membrane receptor and enhances dopamine release and dopamine mediated behaviours. In male rats, estrogen does not affect striate dopamine release, and removal of testicular hormones is without effect. Estrogen influences sensitisation to psychomotor stimulants. The effects of the gonadal hormones on the Striatum and ascending dopamine systems projecting to the Striatum and the Nacc are hypothesised to occur as follows: estrogen induces a rapid change in neuronal excitability by acting on membrane receptors located in intrinsic striate GABAergic neurones and on dopamine terminals. The effect of these two actions results in enhanced stimulated dopamine release through modulation of terminal excitability. These effects of gonadal hormones are postulated to have important implications for gender differences in susceptibility to addiction to the psychomotor stimulants (Becker, 1999).

In summary, Nacc processes reward on both an integrative and output oriented level using specialised groups of neurones. It evaluates different reward aspects and initiates an adjusted response to them. To do so, it involves Frontal, Limbic and motor-related areas and its various biochemical pathways with dopamine playing a central role. The mammal Nacc is sensitive to drugs of abuse, environmental influences like stress, psycho-pharmaceuticals and shows gender differences, making it a key target in human addiction research.

2.1.3 Prefrontal cortex (PFC)

The PFC is the anterior part of the frontal lobes of the brain, lying in front of the motor and premotor areas. It is an area which volume has increased exponentially in evolution from non-primate mammals to non-human mammals and humans (Uylings, 1990). There is an ongoing discussion, if non-primate mammals, especially rats do have an prefrontal cortex at all (Uylings, 2003), while its has accepted for non-human mammals. Originally there is a cytoarchitectonic definition of the PFC by the existence of a cortical granular layer IV (Campbell 1905, G. E. Smith 1907, Brodmann 1909, von Economo and Koskinas 1925); this does not apply to non primate mammals. There also is a functional definition as the PFC is the area to where the mediodorsal nucleus of the thalamus projects (Rose 1948), this model is still accepted today.

The PFC influences emotional, social behaviour and decision making. This leads to the hypothesis that it is involved in reward processing and classical conditioning (Schultz,

2000). Lesions of the PFC disturb decision making in non-human mammals (Pears, 2003). It also disrupts features in conditioned re-inforcement like acquisition of a new response and sensitivity to conditioned stimulus omission (Pears, 2003). A single neurone study revealed the PFC of the macaque to react to magnitude of expected reward. In this study, a cue signalled whether a small or large liquid reward would accompany a correct response. Many neurones in this area responded more frequently when the monkey expected a larger reward (Leon, 1999).

2.1.4 Amygdala

The rodent and primate amygdala is a central part of the Limbic system and been connected to emotion- and memory modulating functions. In single neuron studies the amygdala of primates was able to recognise the affective significance of a reward. It was active upon novelty of an object and modality specification when different kinds of reward were presented, making it crucial for classical conditioning (Nishijo, 1988). In concordance to that, amygdala-lesioned monkeys had disturbed food preferences while amygdala-lesioned rats exhibited a reduction in responding on the lever providing a conditioned reinforcer (Cador, 1989). Compared to the specialisation of Nacc neurones in rats, the lateral amygdala of rats presents 3 similar groups of neurones with special firing patterns. Lateral Amygdala neurones could be subgrouped into, 1. neurons firing anticipatory/preceding the reward (PR); 2. neurons that exhibit activation after response (RFE) and 3. neurons that showed depressed firing rates after response (RFI). Given a cocaine-associated audio-visual cue inbetween a lever re-inforcement session, PR and RFI neurones were not activated by the stimulus. In contrast, RFE neurones were significantly activated by the audio-visual cue (Carelli, 2003).

2.2 Neurochemistry of the mammal reward system

Exhibitory and inhibitory neural transmissions connect reward relevant areas such as the Midbrain, Striatum, Limbic and Frontal areas. The most important are dopamine, GABA, acetylcholine, glutamate, serotonin, opioids, noradrenaline and the hormones estrogen and melanin. In rats, three major transmitter systems are involved in drug reward processing: Dopamine, opioid and GABA (Koob, 1992). Transmitters, their related genes and regulators influence each other in complex ways. Drug application has been studied extensively in animals to understand pharmacological aspects of drugs of

abuse. Any hedonic drug has its implications to the reward system and may change it transiently or chronically.

2.2.1 Dopamine

Dopaminergic transmission appears very early in evolution. Dopamine regulates simple systems like in nematodes such as C. elegans. In mammals, dopaminergic transmission can be divided into different systems:

Central dopaminergic transmission:

1. Midbrain neurones from the VTA and the Substantia Nigra (SN) projecting to the Limbic system and PFC for cognitive functions
2. Midbrain neurones from the SN projecting to the Striatum (Nucleus Putamen) for extrapyramidal motor function and sensory-motor learning
3. The tubero - infundibulary system for milk regulation (dopamine as a prolactin inhibitory factor)
4. The Area Postrema for food regulation

Dopamine is a biogene amine from the group of catecholamines. It is synthesised from tyrosine and processed to DOPA (3,4-Dihydroxyphenylalanin) which becomes decarboxylised to dopamine. It can be further processed into adrenaline, noradrenaline and melanin. Its main metabolites are 3,4-dihydroxyaceticacid and homovanilic acid.
Dopamine receptors can be found centrally and peripherally. They are divided in exhibitory and inhibitory and pre- and postsynaptic receptors. Peripheral D1-receptors activate adenylate cyclase (cAMP), causing vasodilatation of abdominal arterioles. Peripheral D2-receptors inhibit adenylate cyclase, inhibiting sympathic activity and reducing aldosterone release. The D1-receptor group (D1 and D5-receptor) are inhibitory to cAMP and are located in the Striatum; the D2- group (D2, D3 and D4 receptor) group activates cAMP and are located frontally and in the Hippocampus.

Dopaminergic transmission is part of in reinforcement systems. A classical computational model of a reinforcement system is the “prediction-error-model” by Schultz. A delivered reward that is better than expected leads to increased firing of phasic dopamine neurons. This peak activity is interpreted as a key function in the

reinforcement progress. If a reward meets the anticipatory magnitude there is no change in dopamine transmission. An omission of an expected reward leads to a depression of firing dopamine neurones. A repetition of an outcome may lead extinction of behaviour (Schultz, 2000). Single neurone studies by Hollermann et al. are consistent with this model: Dopamine neurones activation was activated, when errors were frequent and rewards unpredictable and rewards occurred at unpredicted times. Dopamine neurons activation was reduced as performance was consolidated and rewards became more predictable. Dopamine neurons activation was depressed when rewards were omitted at predicted times (Hollermann, 1998).

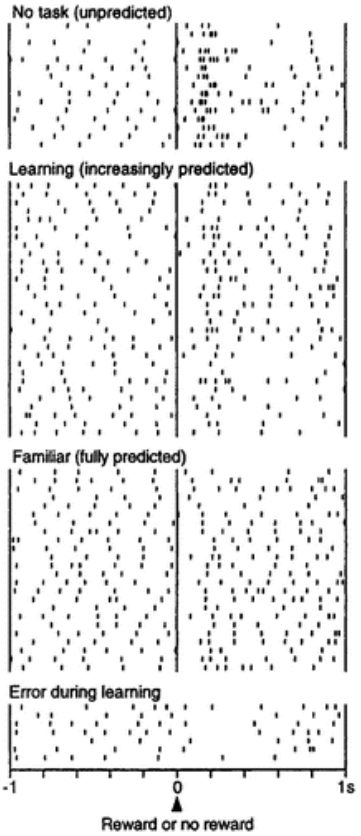


Fig. 2: Coding of reward-prediction error during learning by a single dopamine neuron. No task: The temporally unpredicted occurrence of reward outside of any task induces reliable neuronal activation. Learning: The presentation of a novel picture pair in a two-picture discrimination task leads to uncertain behavioral performance with unpredictable occurrence of reward and dopamine response. (*Top* to *bottom*) Response decreases with increasing picture acquisition (only correct trials shown). Familiar: Presentation of known pictures in same task leads to predictable occurrence of reward and no dopamine response. Error during learning: Error performance with novel pictures leads to omission of reward. (Hollerman, 1998)

Dopamine depletion in mice after chronic cocaine exposure is hypothesised to result from overstimulation of these neurones and excessive synaptic metabolism dopamine (Dackis, 1985). To analyse the role of D-receptors in addictive behaviour, studies with genetic disrupted D2-receptor mice were treated with repeated morphine administration. Behavioural expression of morphine withdrawal was unchanged, but a total suppression

of morphine rewarding properties was observed in a place-preference test, suggesting that lacking D2 receptors diminish rewarding properties.

Drugs of abuse often use various pathways in parallel. Cocaine blocks dopaminergic, serotonin and noradrenalin transporters (DAT, SERT and NET). To solve which of these transporters blockage results in hedonic feeling mice received individual knock-out on each transporter. All mice with individual knock outs did not differ in place preference (a hedonic expression for mice) in comparison to wild type controls. However, mice with a combined DAT and SERT knock-out lost place preference, suggesting that cocaine had no hedonic property to them anymore. This suggests that transmitters in reward processing to substitute each other (Sora, 2001). There are different opinions of what role which receptor plays and publications differ in their findings.

2.2.2 Neurochemical interaction

Other neurotransmitters are found to be involved in reward processing and to interact with accumbal dopamine. These are among others Gamma-amino-butyrate-acid (GABA) (Reynolds, 2002), (Xi, 1998), Acetylcholine (Hikida, 2003), Glutamate (Choi, 2005), noradrenalin (Weinshenker, 2006) and opiates. Various drugs of abuse influence the ventral striatum via agonistic/antagonistic acting substances for these transmitters. Alcohol or benzodiazepines are GABA-agonists known for their strongly addictive properties. (Xi, 1998). Ketamine is a Glutamate antagonist and has been shown to interact closely with accumbal dopamine (Choi, 2005)**.** Cholinergic agonist carbachol and the ACh-inhibitor neostigmine showed effects on the VTA and behaviourally rewarding effects in rats (Hikida, 2003). A substance group that is classically known to have most addictive value for human beings are opiates. The Nacc has a high density of opiate receptors and seems to be central in the re-inforcing properties of opiates (Vaccarino, 1985). We will focus on accumbal dopamine as central transmitter in the underlying system of the prediction error paradigm. It can be speculated that accumbal dopamine and error prediction can be influenced by a complex system of various neurotransmitters including agonists and antagonists of GABA, Glutamate, Acetylcholin, and Opiates. This model below is an example for the complex interactions in hedonic reinforcement for just one transmitter (noradrenaline).

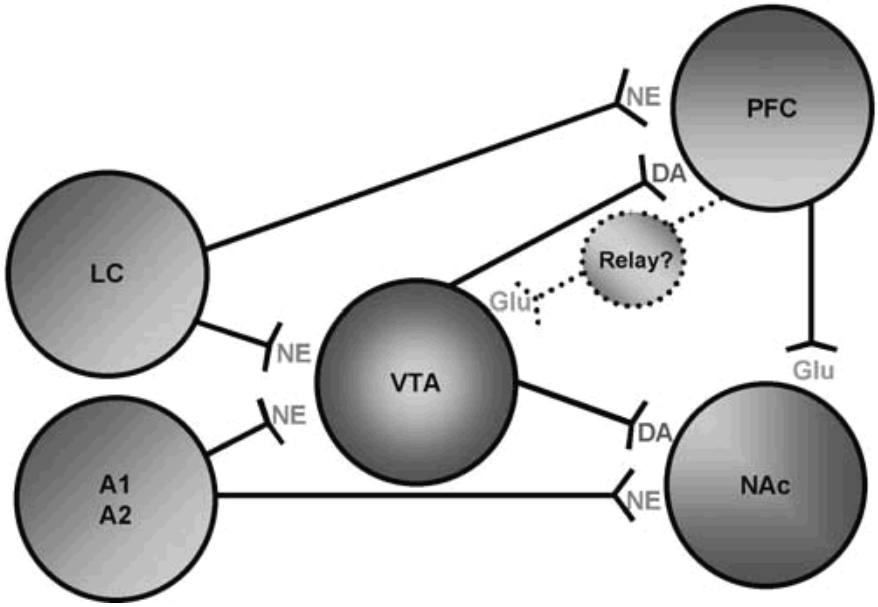


Fig. 3: A wiring and neurotransmitter model for noradrenergic influence of psychostimulant responses. A1 and A2, brainstem noradrenergic cell groups; LC, locus coeruleus; PFC, prefrontal cortex; VTA, ventral tegmental area; NAc, nucleus accumbens; NE, norepinephrine; DA, dopamine; Glu, glutamate. Psychostimulant administration increases extracellular DA in the NAc and PFC and NE in the VTA, PFC, and NAc. NE signaling in the VTA induces burst firing of dopaminergic VTA neurons and increases DA release in the NAc. NE signaling in the PFC activates pyramidal neurons, which release Glu in the VTA resulting in increased excitability and more DA release in the NAc. Many of these noradrenergic inputs are mediated by the a1AR. The convergence of these signals in the NAc and PFC leads to psychostimulant-induced behaviours via downstream neuronal networks (Weinshenker, 2006).

2.3 Reward processing in humans

2.3.1 Special aspects of reward in humans

Reward processing is a core part of human behaviour. It is embedded in behavioural aspects like motivation, decision making, goal directed behaviour and learning. Furthermore it plays a central role in various psychiatric disorders, making it a central theme in clinical research. While for a long time in evolution reward meant natural things like food and whatever helped to survive, humans developed a high sense of abstraction, making abstract things rewarding. With abstraction a new kind of reinforcement was established, commonly referred to as “secondary reinforcement” in contrast to primary reinforcers (such as sugar). Neural processing structures are still similar to mammal reward related structures and can be artificially influenced. Given the hypothesis that goal directed behaviour is driven by reward expectancy, the list of rewarding properties to humans is as long as the list of human goals. In neuroimaging studies natural rewards, abstract rewards and various substances have been used to activate the mesolimbic reward circuitry.

Simple natural rewards or primary reinforcers that elicited activity in the ventral striatum are: Food (Wang 2002, Volkow 2002, Kelley 2002), (Kringelbach, 2004), fruit juice and water (Berns, 2001) and chocolate (Small, 2001). [Natural] secondary reinforcers are: Visual sexual stimulation (Bocher, 2001), beautiful faces (Kampe 2001, Aharon 2001) and music (Blood, 1999, 2001), humour (Mobbs, 2003) and maternal and romantic love (Bartels, 2004).

By far the most powerful and well analysed secondary reinforcer is money. In neuroimaging studies, money was almost exclusively presented in gambling situations, making gambling a well researched phenomenon (Thut 1997, Bechara 1999, (Zalla 2000, O'Doherty 2001, Breiter 2001, Knutson 2001, Gehring 2002, Akitsuki 2003, Elliott 2003). Money allows an exact quantification, thus it is most useful for complex computational models. Even gambling *not* including monetary rewards, like playing a video game showed rewarding properties (Koepp, 1998). Other complex abstract rewarding stimuli that involve status symbols are visual cues of expensive cars (Erk, 2002).

Substances that act on the mesolimbic system of humans: Nicotine (Stein, 1998), alcohol (Koob 1992, Tupala 2004), caffeine (Daly, 1998), cannabis (Robbe, 2003 [a study with mice]), amphetamine (Rogers 1999, Gifford 2000, Mattay 2003, Knutson 2004), ecstasy/MDMA (Hubner, 1988), (Meyer, 2002 [a study with rats]), cocaine (Breiter 1997, Volkow 2000), (Dackis, 1985) and heroine (Bozarth, 1983 [a study with rats], (Wise 1989, Sell 1999). In alcohol-addicted patients, specific visual cues of alcohol without their administration could activate reward-related structures (George 2001, Heinz 2004).

Even though these substances result in a common pathway, i.e. activation of the ventral striatum, their initial mechanisms of triggering hedonistic feelings differ *largely*. **Nicotine** binds are various places in the CNS and SNS resulting in complex pathway with elevated adrenaline and dopamine levels as a key function. In the CNS it binds at nicotinic acetylcholine receptors to increase dopamine in the ventral striatum; in the SNS nicotine acts on the sympathetic nervous system via splanchnic nerves to the adrenal medulla, stimulates the release of epinephrine (Yoshida, 1994). **Alcohol** interferes with membrane proteins of ion channels of neurons of the CNS. It acts as an

agonist on GABA receptors and an antagonist of NDMA receptors (Tiurenkov, 2011). The relaxing properties have been mostly explained by the agonistic properties on GABA, a powerful inhibitory transmitter of numerous pathways. The rewarding and activating effects of **caffeine** are complex and object to discussion. Caffeine is a nonselective antagonist of adenosine receptors. The caffeine molecule is structurally similar to the aglycone of adenosine, adenine, and is capable of binding on the surface of cells without activating them, thereby acting as a competitive inhibitor (Fisone, 2004). An activation of the ventral striatum may occur via adenosine- (A2A) receptors, which are highly concentrated in the basal ganglia (Huang, 2005). **Cannabis** contains Tetrahydrocannabinol (THC) which binds (among others) to the cannabinoid receptor CB1 and the μ1 opioid receptor in the Nacc. Both pathways are believed to explain the hedonistic value of THC (Lupica, 2004). **Amphetamine** and closely related substances such as **Ecstasy/MDMA** (phenethylamines) have a direct effect on the dopamine release in the Nacc, causing spontaneous and long during euphoria (Wise, 2003). In comparison to this direct trigger, **Cocaine** blocks dopaminergic, serotonin and noradrenalin transporters (DAT, SERT and NET), thus increasing the concentration of these transmitters that have intrinsic rewarding properties (Sora, 2001). **Heroine (diacetylmorphine)** binds (among others) to the μ-opioid receptors in CNS and SNS. This pathway is believed to be crucial for the strong rewarding and addictive properties of morphines among other pathways.

2.3.2 Anatomy and function of the human reward system

The Ventral Striatum and its Nacc play a central role in human reward processing (Robbins 1989, Elliott 2000, Delgado 2000, Knutson 2001, Becerra 2002, Zink 2004), (Zald, 2004). Other relevant structures are Prefrontal (Elliott 2000, Small 2001) and Frontal Cortices (Volkow, 2002), Limbic structures like the ACC, the Amygdala (Robbins 1989, Becerra 2002) and the Hippocampus (Elliott, 2000). Just like in mammals, these structures form a midbrain- extrapyramidal -limbic-forebrain-circuitry. According to our results we will only describe striatal and prefrontal areas in this chapter.

The Ventral Striatum

The Ventral Striatum showed activation to all incentives of the latter chapter.

Some studies suggest that reward experience is the main activator of the Ventral Striatum, but expectancy to reward has also shown to be at least as strong or even more activating. On a higher level of integration, the Ventral Striatum might evaluate magnitude of reward-experience with its expectancy, thus leading to neural network optimisation as a process of learning.

To differentiate the role of the Ventral Striatum in reward processing, different kinds of reward were presented to human subjects. They received a variable ratio (VR) reward schedule with 25% reward rate in which they did not know the outcome of their responses in advance, a fixed ratio (FR) 25% reward schedule in which outcomes were fully predictable, and a sensorimotor control (SC) condition involving similar sensory and motor demands but no rewards. Relative to the SC condition, the FR schedule produced only modest increases in dopamine transmission. In contrast, the VR schedule produced significant increases in dopamine transmission in the left Medial Caudate Nucleus while simultaneously producing significant decreases in other areas of the Caudate and the Putamen. These data indicate: (1) alterations in dopamine transmission even after controlling for sensorimotor features and (2) the complex and regionally specific influence of VR schedules on dopamine transmission (Zald, 2004).

In order to analyse the processing of incentives, participants were given trials of card guessing with high incentive (feedback including money and punishment) and low incentive (feedback including information about accuracy). Activity in the Caudate was strongly influenced by different incentive periods. The hemodynamic response was characterised by a larger rise at the onset of trials and larger differences between positive and negative feedback during periods of high incentive (Delgado, 2004).

The Ventral Striatum signals errors in the prediction of rewards. That hypothesis is concordant with the high activity in unexpected reward related events, having a “positive prediction error”, being better than expected. This hypothesis was tested in humans with an operant conditioning paradigm for delivery of fruit juice, along with a control experiment in which juice was substituted with a neutral visual stimulus. A local estimation of activity in the Ventral Striatum showed a significant differentiation when the juice was withheld at the expected time of delivery; this finding was not replicated

in the case of visual stimulation, providing evidence for time-locked processing of reward prediction errors in ventral striatum (Pagnoni, 2002).

Many studies differentiate between reward expectancy and actual reward experience. Results by a study by Knutson indicated that while anticipation of reward activated the Ventral Striatum, actual reward outcomes activated the VMPFC. Reward anticipation and outcomes may differentially recruit distinct regions that lie along the trajectory of ascending dopamine projections (Knutson, 2001). Berns showed activity in the Nucleus Accumbens to be modulated by the predictability of mildly pleasurable stimuli (fruit juice and water). Activity for rewarding stimuli in both the Nacc and the Medial OFC was greatest when the stimuli were unpredictable. Moreover, the subjects' stated preference for either juice or water was not directly correlated with activity in reward regions, but instead was correlated with activity in sensorimotor cortex. For pleasurable stimuli, these findings suggest that predictability modulates the response of human reward regions, and subjective preference can be dissociated from this response (Berns, 2001).

Nacc activations were observed following financial reward depending on a correct response ("active task") compared to passively received money. The authors suspect such activations were attributed to saliency rather than the motor requirement associated with the active money task. Striate activations were not observed when the money was replaced by inconsequential, non-rewarding stimuli. A follow-up study activated the Nacc in salient, yet *non*-rewarding events. FMRI results reveal increased activation in the Nacc after infrequent (high salience) relative to frequent (low salience) presentation of distracters. These results add to the evidence that the Ventral Striatum also encodes non-rewarding salient events (Zink, 2003, 2004).

The Prefrontal Cortex (PFC)

The Prefrontal Cortex is well connected with association areas of all sensory modalities, Limbic structures, various other Prefrontal Cortical regions and subcortical nuclei. This brain region can serve to integrate the physical and emotional attributes of a stimulus object and establish a motivational value based on estimation of potential reward (London, 2000). Summarising various studies, Prefrontal areas process aspects of decision making, impulse inhibition, reward detection and are also involved in

addiction-related behaviour like craving and withdrawal. The fact the Prefrontal lesions impair decision making has been shown early and repeatedly. Comparative to rodents and primates, the human PFC can be subdivided into various regions such as the Orbital FC (OFC), Ventromedial PFC (vmPFC) and dorsolateral PFC (dlPFC).

Decision Making and Impulse control

Frontal lobes are involved in tasks ranging from making binary choices to making multi-attribute decisions that require explicit deliberation and integration of diverse sources of information. In categorising different aspects of decision making, a division of the PFC into three primary regions is proposed:

1. The OFC and vmPFC are most relevant in decisions based on reward values; they contribute affective information regarding decision attributes and options.
2. The dlPFC is critical in making decisions that call for the consideration of multiple sources of information, and may recruit separable areas when making well defined versus poorly defined decisions (Krawczyk, 2002).

Not all studies agree to this, but studies agree that prefrontal areas are involved in different levels of decision making among other functions. In drug and lesion studies, activation is often found in different subgroups, with some showing activation and other depression, indicating their specialisation. In studies that investigate decision making abilities some lateralization has been found. A study of patients with unilateral lesions to the PFC showed severe disruptions of everyday decision-making, with concomitant effects on social and occupational functioning. In more detail, patients with **right frontal** lesions preferred risky behaviour in the Iowa Gambling Task, and differed significantly from left frontal and control subjects. Within the **right frontal** group, the preference for the risky decks was correlated with the total lesion volume and the volume of damage outside of the vmPFC region (Clark, 2003).

To show the severity of impaired decision making due to PFC in everyday life and possible vulnerability to addictive behaviour, a study with patients with lesions to the vmPFC were tested on a gambling task and other standardised psychological interviews. Results revealed significantly low emotional intelligence and poor judgement in decision-making as well as disturbances in social functioning, in spite of normal IQ and the absence of psychopathology based on DSM-IV criteria (Bar-on, 2003).

Cocaine can cause prefrontal lesions. A study tested whether 25-day-abstinent cocaine abusers show alterations in normalised cerebral blood flow (rCBF) in the OFC during the Iowa Gambling Task. Cocaine abusers showed greater activation during performance of the Iowa Gambling Task in the **right** OFC and less activation in the dlPFC and left medial PFC compared to a control group. Better gambling performance was associated with greater activation in the **right** OFC in both groups. Also, the amount of cocaine used was negatively correlated with activation in the left OFC. Cocaine abusers show persistent functional abnormalities in prefrontal neural networks and related decision impairment (Bolla, 2003). Concordant with making bad decisions of PFC-lesion patients, there seems to be a loss of regret in these patients. Patients with OFC-lesions did not report regret or anticipate negative consequences of their choices (Camille 2004, Carmichael 2004). In summary, PFC lesion studies show impaired decision making and impulse control loss. Some studies show direct activity of prefrontal areas in rewarding situations. The right dlPFC cortex shows activity in extraordinary winning and losing situations (Akitsuki, 2003), the OFC in unpredicted winning money and the vmPFC showed activity in relation to increasing amounts of reward and penalty (Ramnani, 2004). The OFC presented activation in typical states or symptoms of addiction (in addicted subjects) like intoxication or craving and is deactivated during withdrawal (Goldstein, 2002). Volkow identified hyperactivity in OFC in craving amongst several other structures (Volkow, 2002).

The Amygdala

The human Amygdala is located in the medial temporal Lobe. It is a central part of the Limbic system and has abundant functions and is connected to various and widespread brain parts. Here we focus on reward related functions of the amygdala. The amygdala is well connected to the PFC and the Nacc. It plays a crucial role in emotional learning and memory modulation. Arousal and fear-related behaviour is believed to be controlled in the amygdala. Bilateral lesions in this region have shown to result in loss of fear and risky behaviour (Coppens, 2010).

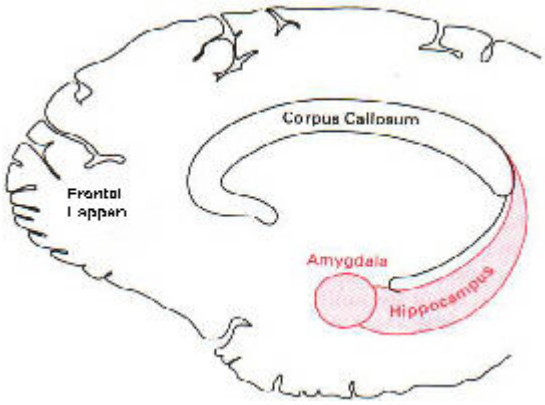


Fig. 4: The amygdala positioned at the anterior temporal lobe (courtesy by Prof. Dr .Dr. Gerhard Roth, Lindau)

The sublenticular extended dorsal part of the amygdala (SLEA) has been recognised to be specialized in emotional processing. It was found to be activated upon positive as well as negative facial expressions (Whalen, 1998), aversive (Phan, 2003) but also positive visual stimuli (Liberzon, 2003) Overall the SLEA appears to encode negative expectations rather than positive ones (Abler, 2006). A hyperactive amygdala was found in depressed patients using resting state fMRI (Drevets, 2000). This is in concordance with a gambling study by Yacubian that found the amygdala (in combination with the Nacc) to be active only in negative anticipation and outcome events, but not in positive ones (Yacubian, 2006). Vegetative reactions to fearful stimuli are processed by the amygdala and elicit symptoms such as freezing (immobility), tachycardia, increased respiration, and stress-hormone release (Amunts, 2005).

2.3.3 Dysfunction of human reward processing structures

Dysfunctions of reward processing structures have been brought into connection with various psychiatric disorders. Almost all psychiatric disorders have been associated with dysfunctions in reward processing structures: Alcoholism, all other substance addiction disorders, impulsive and compulsive behavioural-disorders, **pathological gambling**, sex addiction, ADHD, Tourette's syndrome, autism, chronic violent behaviour, posttraumatic stress disorder, personality disorders with a focus on the schizoid/avoidant cluster, conduct disorder and antisocial behaviour (Blum, 2000).

Main foci of a dysfunctional reward system are the dopaminergic structures of the Ventral Striatum and the PFC. Studies suggest that a disturbed striate dopaminergic transmission plays a role in addiction development and maintenance with features like craving and withdrawal. This topic has been approached from different sides.

Deficiencies in the reward system seem to cause addictive behaviour (or addictive behaviour causes the reward system to become dysfunctional) (Self, 2003). Dysfunctions in the brain reward cascade could cause a hypodopaminergic trait and the brain of that person than requires a dopamine recompensation. This trait leads to drug-seeking behaviour. Drug consumption causes a release of dopamine thus healing the abnormal cravings (Blum, 2000).

Volkow presented a human PET study in which elevated dopamine in the ventral striatum is associated with the subjective reports of drug reinforcement. During drug withdrawal in drug abusers she showed significant reductions in D2 receptor density and dopamine release. This hypodopaminergic state could result in a decreased sensitivity to natural reinforcers perpetuating the use of the drug as a means to compensate for this deficit and contributing to the anhedonia and dysphoria seen during withdrawal. Because D2 receptor density reductions are associated with decreased activity in the ACC and the OFC, he postulates this to be one of the mechanisms by which dopamine disruption leads to compulsive drug administration. This is supported by studies that frontal regions become hyperactive in craving. Craving is also associated with activation of memory circuits including the Amygdala (implicated in learning), the Hippocampus (implicated in declarative learning), and the Dorsal Striatum (implicated in habit learning); all of which receive dopaminergic innervation. Dopamine contributes to addiction by disrupting frontal cortical circuits that regulate motivation, drive, and self-control and by memory circuits that increase the motivational salience of the drug and drug-associated stimuli (Volkow, 2002).

With chronic cocaine use, neurotransmitter and neuroendocrine alterations occur. Dopamine depletion is hypothesised to result from overstimulation of these neurones and excessive synaptic metabolism of the neurotransmitter (Dackis, 1985). Chronic cocaine consumption also produces increases in brain reward thresholds that may reflect the "dysphoria" and anhedonia associated with cocaine dependence and suggests a dysregulation of brain reward systems possibly involving dopamine (Koob, 1992). Voxel-based-morphometry (VBM), a method to show differences in volume of certain brain areas, showed actual „brain shrinking” in cocaine users. Grey matter concentration in the VMPFC, ACC, Antero-Ventral Insular, and Superior Temporal Cortices of cocaine addicted patients was decreased in comparison to controls. The average

percentage decrease in grey matter concentration within a region ranged from 5% to 11% while white matter concentration did not differ between the groups (Franklin, 2002).

Besides extrinsic damages to the reward system there are various factors that define the constitution of the system itself. Various genes have been identified to play a role in reward processing structures. The most popular ones are genes for dopamine-receptors, DRD 2 (Berman, 2002), (Duan, 2003), DRD 3 (Spangler, 2003), DRD 4, (Benjamin, 2000), (Schinka, 2003), dopamine transporter DAT (Uhl, 2003), but also the 5-HT2C serotonin receptor (Ebstein, 1997) serotonin transporter SERT (Uhl, 2003); the serotonin transporter promoter region (5-HTTLPR), catechol-O-methyltransferase (COMT) (Benjamin, 2000) and finally monoaminooxidase MAO-A and MAO-B genes (Ibanez, 2000). Mutations and polymorphisms of these genes are believed to play a role in reward system related disorders and addiction related personality traits. The DRD genes are likely to influence receptor density and affinity in the Ventral Striatum, making them very interesting for addiction research. They are used to explain heritability of various psychiatric disorders. The distribution and state of dopaminergic structures, especially receptors and their genetic correlate have been connected with different personality traits like novelty seeking, risk taking and harm avoidance-behaviour.

2.4 Gambling and pathological gambling

2.4.1 Introduction

Gambling is a human trait, which can be found in most humans, places, time and geography. It exist from the ancient Greek dice made of bones to today's Japanese Pachinko gamblers, from boys playing game consoles to grandmothers card game evening. The role of gambling to the individual reaches from passionate enjoyment to be forced to commit suicide.

Modern gambling represents a refinement of risk and chance, which draw upon the faculties of judgement and novelty-seeking. Neurobiological systems guiding choice and behaviour have evolved to maximise chances for survival under hunter-gatherer conditions, and modern gambling may represent a departure from these circumstances

(Spinella, 2003). Motivations in gambling are complex. While making money is the classical goal, it appears that the process of taking a risk itself is what makes gambling so attractive. The process of expectancy and experience is correlated to arousal and sensation seeking and can be considered the addictive part in gambling. The line between recreational gambling and pathological gambling is continuous. Also, some forms of gambling are quite accepted and other highly stigmatised. While billions of people gamble for fun and do not suffer from it, a certain amount of these people lose control about gambling and become pathologic gamblers. The individual and societal dimensions of pathologic gambling are severe. Common personal consequences include family disruption, unemployment, financial break down, involvement in illegal activities and incarceration leading to increased rates of depression and suicide rate. The societal impact includes missing work and high costs of treatment. Duvarci compared social gamblers to pathologic gamblers. He showed that pathologic gamblers gambled to recover their losses, experienced craving for gambling more often, gambled more often to obtain relief from disturbing emotions, harboured more irrational and unrealistic cognitions to rationalise their gambling behaviour and suffered more emotionally, financially and socially as a result of their involvement in gambling in comparison to social gamblers (Duvarci, 2000).

There is no single conceptual theoretical model that adequately accounts for the multiple biological, psychological and ecological variables contributing to the development of pathological gambling. Pathologic gambling can be analysed by the triangular model of addiction. Regarding gambling, this model states that 1. *forms* of gambling, 2. *availability* of gambling/social acceptance and 3. *features of the individual* gambler (e.g., an individual's personality, biochemistry, psychological states, and cognitions) are involved in development, maintenance and severity of addiction. The definition of pathological gambling as a psychiatric disorder is relatively new. The American psychological association classified pathologic gambling in the DSM-III for the first time in 1980. Upon today it is not clear into which psychiatric-diagnostic framework pathologic gambling belongs. The interpretation if pathologic gambling is rather an addiction or an impulse control disorder has fundamental implications for treatment and payment of therapy by health insurance.

2.4.2 History

The existence and ambiguity of gambling appears to be as old as humanity itself. Ivory dice from 1573 b.c. have been found in Egypt (Wykes, 1967) and the Greek Themistocles warned in 525 b.c. that people who work for the government should never gamble. While the Roman culture fully integrated gambling into everyday culture, religions like the Islam condemned gambling and called it evil. Around 1450 playing cards got fashionable in Europe and this was soon followed by laws to limit or prohibit gambling.

In 1561, the Flandic doctor and philosopher Paquier Joostens published the first detailed description about gambling as a disease (Reprint Bauer, 1995). This paper is believed to be one of the first scientific descriptions of addiction in western culture (Petersmann 1995). Lottery started to be popular in the 16th century to be followed by roulette in the 17th century. The philosopher and mathematician Blaise Pasqual had invented the latter one which is believed to be the most passionate and immaculate way of gambling (Gizycki, 1970). When all forms of gambling were prohibited in France in 1837, many roulette casinos moved to Germany. It was there that the Russian author Dostojewski gambled and described his adventures in the famous novel "Der Spieler" in 1866. In Germany gambling was then outlawed as well in 1868 until the Nazi regime legalised it again in 1933 under certain conditions. A very popular form of gambling is the slot machine, which was introduced in 1895. Today state controlled gambling is legal in most western countries and influences their culture in many ways. Forms of gambling follow closely technical development and computer and internet have become important tools of modern gambling. The impact of gambling is underestimated, evidence of how deep gambling is embedded in our daily culture can be seen almost everywhere. In Germany the numbers of the lottery are published in all important media, hour by hour.

2.4.3 Legal Issues

In the European Union the handling of gambling is left to the individual countries. The German law states that the gambling must be in the hands of the government (§284 StGB). This gambling monopoly has the reason "to control the economic exploitation of the passion for gambling" (BGH St11, S. 209). By German criminal law, gambling is defined as:

- winning or losing a game is decided by random chances
- the bet/ invested financial amount may not be insignificant

- the gambler has to invest money to participate in the chance of winning (Schönke, 1997)

However, “not insignificant” is not well defined. Meyer believes the government not to control the financial exploitation of gamblers, but expands gambling opportunities and primarily tries to earn money with the gambling monopoly. (Meyer, “Spielsucht”, Springer Verlag, 2000)

2.4.4 Forms of gambling

Roughly, today’s western gambling can be divided into three groups.

1. Lottery: Various forms of lottery exist and represent a form of gambling with small bets, high availability and social acceptance. Most participants are generally not considered pathologic. Lottery has the highest prevalence in public of the different forms of gambling.

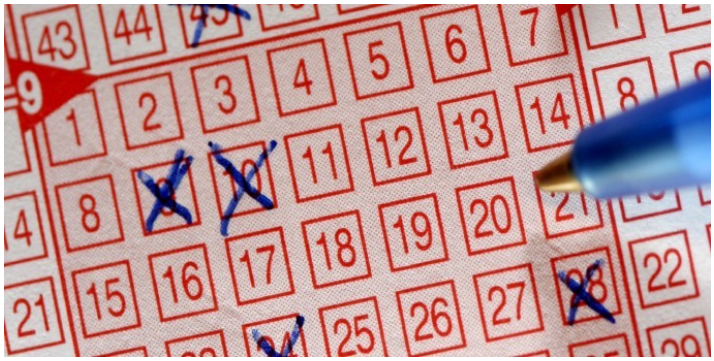


Fig. 5: The most common form of gambling: Lotto (www.n24.de)

2. Slot machines: They can be found in most pubs or specific slot machine-places and are also highly available. The bets are restricted governmentally to be low, but with manipulation larger amounts of money can be lost. This form of gambling is somewhat stigmatised and the percentage of gamblers that are pathologic is considerably high.

Fig. 6: A common sight: The author trying slot machines (www.planet-wissen.de)

3. Casinos: The classical forms of gambling like roulette and card games are played in state owned casinos. The threshold to participate is higher (e.g. dress code, ID-check), but the individual bets are high, making casinos the most important income source to the government.

Fig. 7: The classical form of gambling- taking high stakes at roulette (www.taz.de)

Most pathologic gamblers play various forms of gambling: “Participation in a greater number of types of gambling is strongly predictive of gambling pathology” (Grant, 2001). Besides these official forms of gambling, there are numerous games which mostly represent illegal forms of gambling. In combination of organised illegal gaming there is a huge gambling black-market. There are no statistics about this, but it is believed to play a big role. Gambling related activities like computer games and game consoles have become a major way to spend spare time for adolescents and form a huge gaming industry. Trading at the stock-exchange can be very speculative and has often features of pathologic gambling. The “dot-com bubble” of IT-company stock options

attracted many people to trade like bets and caused major losses for many people. Both activities must be seen in the context of pathologic gambling and show the widespread of gambling like behaviour.

Slot machines	Casinos	Lottery	Other
21%	40.3%	30%	8.7%

Table 1: Percentages of revenues of different forms of Gambling in 2003 (Meyer, Jahrbuch Sucht, 2004)

2.4.5 Economics

In the EU and US the government has the monopoly of gambling. Historically it is believed that this is the only way to control gambling and make it safer. For western countries gambling is a major income resource. For Germany, the turnover of the gambling market has risen to 27.54 billion Euros in 2003 (rate of increase: 0,6%). The gambling revenue of Germany ranked above the alcohol revenue. The government increases gambling availability in various ways and thus causes an increase in pathologic gambling (Meyer, Jahrbuch Sucht 2004). Increasing rates of legalised gambling are related to the prevalence of pathologic gambling (Pietrzak, 2003). A study showed the prevalence of problem gamblers to be much higher in regions with newly opened casinos (16%) than in other regions (Grant-Stitt, 2000).

1970	1975	1980	1985	1990	1995	2000	2003
658	940	1522	1905	2478	3479*	4371*	4409*

Table 2: Governmental revenues from gambling in million Euros (*including the new states of Germany, Meyer, Jahrbuch Sucht, 2004)

2.4.6 Diagnostics

The two diagnostic guidelines for psychiatric diseases ICD-10 and DSM IV define pathological gambling slightly different. In ICD-10 it is listed amongst personality disorders in the subsection of impulse control disorders. Here it is mentioned amongst disorders such as kleptomania, pyromania or trichotomania. However, diagnostic criteria are derived from substance addiction disorders and include craving and withdrawal. The basic criteria in ICD-10 for pathological gambling (F63.0) are:

1. Repetitive and permanent gambling
2. Continuous and intensified gambling in spite of negative social consequences, like poverty, disturbed family relations and damage to personal background.

ICD-10 has 3 differential diagnoses which are normal gambling, excessive gambling of manic patients and gambling of people with patho-social personality. The criteria in DSM-IV for pathological gambling are:

A. Persistent and recurrent maladaptive gambling behaviour as indicated by five or more of the following:

(1) is preoccupied with gambling (i.e., preoccupied with reliving past gambling experiences, handicapping or planning the next venture, or thinking of ways to get money with which to gamble).

(2) needs to gamble with increasing amounts of money in order to achieve the desired excitement

(3) has repeated unsuccessful efforts to control, cut back or stop gambling

(4) is restless or irritable when attempting to cut down or stop gambling

(5) gambles as a way of escaping from problems or of relieving a dysphoric mood (e.g., feelings of helplessness, guilt, anxiety, depression)

(6) after losing money by gambling, often returns another day to get even ("chasing" one's loses)

(7) lies to family members, therapist, or to others to conceal the extent of involvement with gambling

(8) has committed illegal acts such as forgery, fraud, theft, or embezzlement to finance gambling

(9) has jeopardised or lost a significant relationship, job, or educational or career opportunity because gambling

(10) relies on others to provide money to relieve a desperate financial situation caused by gambling

B. The gambling behaviour in not better accounted for by a manic episode

DSM IV has 4 differential diagnoses for pathological gambling, which are social gambling, professional gambling, excessive gambling in a manic episode and gambling of people with antisocial personality disorder (double diagnosis possible).

The DSM-IV criteria are a reliable diagnostic tool. Stinchfield measured reliability, validity, and classification accuracy of the DSM-IV diagnostic criteria for pathological gambling, finding them to be reliable and valid. With a standard cut-off score of 5,

DSM-IV criteria yielded satisfactory classification accuracy results; however, a cut-off score of 4 made modest improvements in classification accuracy and, most important, reduced the rate of false negatives. The DSM-IV diagnostic criteria for pathological gambling, when operationalized into questions, demonstrated satisfactory reliability, validity, and classification accuracy, and a cut-off score of 4 improved diagnostic precision (Stinchfield, 2003).

For a more detailed diagnosis the most commonly used assessment instrument is the DSM-based, 20-item South Oaks Gambling Screen (SOGS) (Petry, 1999). The SOGS is a 20-item questionnaire based on DSM-III criteria for pathological gambling. It may be self-administered or administered by non-professional or professional interviewers. A large validation study showed adequate stability and internal consistency reliability (Poulin, 2002). The nosological classification of pathological gambling as an impulse disorder has been criticised by many authors that believe pathological gambling to be part of addiction disorders (Dannon, 2010). Symptoms like craving and withdrawal that often occur in pathological gambling are typical for substance based addictions and support that thesis.

2.4.7 Epidemiology

It is complex to give a complete view on the figures and statistics of gambling and pathological gambling. The definition of problem-gambling, pathological gambling and social pleasure-gambling differs and most pathological gamblers will not admit their true gambling behaviour. There are geographical tendencies in gambling due to different laws and cultures. For example, gambling is more popular in former West Germany than in the former East Germany; in the EU gambling in the Mediterranean area is more common than in northern Europe. Overall pathologic gambling is a severe psychiatric and cultural problem with increasing prevalence.

For Germany, slot machine gamblers form the biggest group amongst pathological gamblers, with a total number of estimated 80,000-140,000. The frequency of outpatient treatment of pathological gamblers has not changed much in the last years; their proportion in the centres is 2.3 % as in the previous years, while the number of treated patients in inpatient centres rises up. Stiftung Warentest found in 1992 that 1% of Germans having gambled a slot machine on a regular base (Stiftung Warentest, 1992).

Another study (Bühringer, 1997) found 33 % of west Germans and 9.9 % of east Germans with at least one time prevalence of gambling. The same study states that 8% of West Germans and 6.9 % of East Germans are active gamblers, meaning that they have gambled at least once within the last 3 month.

Country	**Study/Year**	**Sample-size**	**Risk gambler**	**Pathological Ga.**
Germany	Meyer/2003	Estimation		1% - 1.75%
	Bühringer/1997	estimation	8% (west) 6.9% (east)	
Spain	Becoña /1997	1615 (> 18 a)	1,6%	1,7%
Swiss	Bondolfi/2000	2526 (> 18 a)	2.2%	0.8%
United Kingdom	Griffiths/2007	2014 (> 16 a)	1.2%	0.8%
Sweden	Volberg/2001	7139 (15-74 a)	2.7%(lifetime-pr) 1.4% (point-pr)	1.2%(lifetime-pr) 0.6%(point-pr)
Norway	Götestam/2003	2014 (> 18 a)	0.45%	0.15%
Romania	Lupu/2002	500 (14 -19 a)		
USA	Petry/ 1999			1.4%(lifetime-pr) 5.1% (point-pr)
USA	Lesieur/ 1987	892(high-school)		5.7% (point-pr)
Hong Kong	Wong/2003	2004(> 18 a)	4%	1.8%
New Zealand	Volberg/1994	4053 (> 18 a)	4.2%	2.7%

Table 3: International comparisons of prevalence (pr) of pathological gambling

International studies give more details on prevalence and forms of gambling and show pathologic gambling to be a global problem. Past studies indicate an increase in overall gambling participation in the U.S., and large increases in rates of participation in lottery and casino gambling (Welte, 2002). Another US study found that 91% of the students had gambled at least once in their lifetime, 86% gambled in the last year and 32% gambled at least once a week; 5.7% of the students showed clear signs of pathologic gambling. The pathological gambling signs index was found to be correlated with sex, parental gambling problems, grade average, and the extent of gambling by the student (Lesieur, 1987). A Hong Kong survey analysed the prevalence of problem and pathological gambling. Significant differences between the survey sample and the

respondents showed the difficulties of making surveys about stigmatised issues. Results showed that 4.0 % and 1.8 % of the respondents could be classified as problem and pathological gamblers. The predictors of problem and pathological gambling were sex, education level and family income (Wong, 2003).

In adolescents, addictive playing (e.g. computer games) is a young form of pathologic gambling. A study on a sample of the Norwegian youth population showed weekly players of computer games to be 63.3 %. 4.2 % of the boys and 1.1 % of the girls could be described as exhibiting "pathological playing". Of the weekly gamblers, 4.2% fulfilled 5 criteria for pathological playing, and an additional 15.5% 3 to 4 criteria, i.e., at-risk playing. This indicated that frequent gaming on computer games without money rewards may be related to problematic playing even though no monetary reward is involved (Johansson, 2004).

2.4.8 Risk factors

Gender

Gender was found to be a key risk factor. Studies on male and female prevalence on pathologic gambling show males are 3 – 4 times more likely to gamble than women. Female-male ratios are 1: 4.6 in Romanian teenagers (Lupu, 2002), or 1 : 3.81 in Norwegian youth population regarding pathological playing (Johansson, 2004). However, many authors do not see absolute differences in male and female gambling behaviour, but in specific gambling features such as frequency and choice of game. Men and women were equally likely to gamble in the past year, but men gambled more frequently and had larger wins and losses, particularly on sports betting and games of skill (Welte, 2002). Grant analysed details of the demographic and phenomenological differences in male and female pathologic gamblers. He found that men had an earlier age of onset of gambling behaviour, while women progressed to pathological gambling sooner after beginning to gamble. In terms of gambling behaviour, men were more likely to engage in blackjack, cards, sporting events, and the track, whereas women played slot machines and bingo. Both groups were equally likely to seek treatment, but Gamblers Anonymous and outpatient therapy were reported equally ineffective in reducing gambling symptoms (Grant, 2002).

Ibanez could present some replications and differences in her study. 66% of men versus 25% of women had gambled in adolescence. Women had a later age at first bet and a faster evolution of the disorder. Male and female pathologic gamblers had similar gambling severity and overall rates of psychiatric comorbidity. However, male pathologic gamblers had higher rates of alcohol abuse/dependence and antisocial personality disorder, whereas women had higher rates of affective disorders and history of physical abuse. There are substantial gender differences in the clinical presentation and comorbidity of pathological gambling (Ibanez, 2003).

Age

Adolescents gamble more often. Even though most pathologic gamblers that seek and get treatment are older than 18 (Black, 1998), the prevalence of pathologic gambling is suspected to be higher in adolescents. The prevalence of problem and pathological gambling in adolescence and young adulthood has been found to be two- to fourfold higher than in adulthood (Chambers, 2002); Albers states young age to be a risk factor for slot machine gambling (Albers, 1997), Pietrzak describes the difference in prevalence is described as high as 6% of adults and 20% of adolescents (Pietrzak, 2003). Volberg, too, describes being under 25 as a risk factor (Volberg, 2001). Welte found that the rate of past year gambling declines with age, but extent of gambling involvement among gamblers does not vary with age (Welte, 2002). Possible reasons for that are given by a study by Chambers. He reports that neurodevelopmental events during adolescence occur in brain regions associated with motivation and impulsive behaviour. Immaturity of frontal cortical and subcortical monoaminergic systems during normal neurodevelopment underlay adolescent impulsivity as a transitional trait-behaviour. An exploration of the developmental changes in neural circuitry involved in impulse control has significant implications for understanding adolescent behaviours and treating problem and pathologic gambling among youths (Chambers, 2003).

Social Status

Numerous studies suspect low economic status (Welte, 2002), unemployment (Hall, 2000), (Volberg, 2001) and educational status to be a high risk factor for pathological gambling. This could also be shown for racial minority groups (Welte, 2002); foreigners (Volberg, 2001) or not well integrated people. Growing up as a delinquent can be a risk factor (Pietrzak, 2003), (Hardoon, 2004), just as well as being incarcerated (Hall, 2000).

For Germany, Albers showed participation in gaming machines is higher for unemployed and less educated adults (Albers, 1997).

Family History

Gambling of relatives increases the risk for pathological gambling. Studies that analysed family history showed a clear risk factor in having relatives that are pathological gamblers (Lesieur, 1987), (Eisen, 1998), (Pietrzak, 2003). The majority of the subjects (58%) had at least 1 first-degree relative who also exhibited symptoms of problematic gambling behaviour (Grant, 2001). A twin study showed that inherited factors explain between 35% - 54% of liability for five individual symptoms of pathological gambling behaviour. In addition, familial factors explain 56% of the report of three or more symptoms of pathological gambling and 62% of the diagnosis of pathological gambling disorder (Eisen, 1998). Psychosocial difficulties associated with problem gambling include poor perceived familial and peer social support, substance use problems, conduct problems, family problems, and parental involvement in gambling and substance use (Hardoon, 2004).

2.4.9 Comorbidities

Many pathological gamblers suffer severe psychiatric comorbidities. The most dominant is drug abuse with at least to 64 % lifetime prevalence (Black, 1998). There is a focus on alcohol (Bondolfi, 2000), (Welte, 2002), (Pietrzak, 2003), cocaine (Hall, 2000) and nicotine addiction (Hall, 2000). Impulse control disorders were also common among pathological gamblers, especially compulsive buying and compulsive sexual behaviour (Black, 1998), (Grant, 2002).

87 % of all pathologic gamblers are suspected to suffer a personality disorder, the most common being obsessive-compulsive, avoidant, schizotypical, and paranoid personality disorders. There is also a relatively high rate of antisocial personality disorder (Black, 1998), (Slutske, 2001), (Hall, 2000) and cluster B disorders (Kaminer, 2002). Also, child conduct disorder is also a risk factor for pathological gambling (Slutske, 2001). Black reports up to 40% of all pathological gamblers to show a lifetime anxiety disorder (Black, 1998). Finally affective disorders (up to 76% lifetime prevalence [Black 1998], [Decaria, 1996]) and suicide attempts (Decaria, 1996), (Kaminer, 2002) are co-diagnosed with pathological gambling.

Addiction

There are two ways to study comorbidities of pathological gamblers and addicted patients. One can either analyse the pathological gamblers on their addictive behaviour, or addicts on their gambling behaviour. Many studies pursued the latter way. Lesieur questioned patients in an alcoholism treatment facility about their gambling behaviour. 9% were diagnosed as pathological gamblers and an additional 10% showed signs of problematic gambling. 5% of the patients abusing only alcohol, 12% of those with alcohol and another drug in combination, and 18% of those with other drug abuse problems (but without an alcohol component) showed clear signs of pathological gambling. 11.5 % of males and 2% of females were classified as pathological gamblers. The index was also significantly associated with parental gambling (38% of the children of pathological gamblers were pathological gamblers themselves). Gambling by siblings, alcoholism in the father, gambling prior to age 20, greater amounts of gambling for more money were also positively correlated with the index (Lesieur, 1986). Studies range from only 1% of adolescent substance abusers being pathological gamblers (Kaminer, 2002) to 21% of methadone patients to be probable pathological gamblers (Spunt, 2002). Cocaine-dependent patients had a lifetime occurrence rate of pathological gambling of 8 % and a past month occurrence of 3.8%. Onset of pathological gambling preceded the onset of cocaine dependence in 72 % of the patients. Patients with pathological gambling did not differ significantly from other patients (in length of treatment or proportion of cocaine-positive urine samples). Pathological gambling is substantially more prevalent among cocaine-dependent outpatients than in the general population (Hall, 2000). Maccallum questioned pathological gamblers about their addiction history. Again, the rates for substance use disorder within this sample are higher as compared to general population figures (Maccallum, 2002).

Impulse control disorder

A study by Grant investigated the rate of impulse control disorders (OCD) among pathological gambling and examined the relationship of comorbidity to gambling severity. 22.9% reported a comorbid impulse control disorder, most commonly compulsive sexual behaviour and compulsive buying. Subjects with comorbidity reported significantly greater intensity of urges and thoughts related to gambling, and

greater interference and distress secondary to gambling urges and thoughts. Impulse control disorders appear common among pathological gamblers and are associated with more severe gambling symptoms (Grant, 2002). Another study investigated the similarities and differences in the personality dimensions of pathological gambling and OCD. Pathological gamblers, subjects with OCD and normal controls were assessed on three personality dimensions: novelty seeking, reward dependence, and harm avoidance. Compared with OCD subjects, pathological gamblers subjects expressed significantly greater novelty seeking, impulsiveness, and extravagance. Pathological gamblers also reported less anticipatory worry, fear of uncertainty, and harm avoidance than the OCD subjects. Compared with controls, pathological gamblers expressed greater novelty seeking, impulsiveness, and extravagance. These results suggest that the personality dimensions of pathological gamblers may differ significantly from both those of OCD patients and normal controls (Kim, 2001).

Depression and suicide

A major depressive disorder is likely to occur in 76 % of pathologic gamblers, with recurrent depressive episodes likely to occur in 28 % of pathologic gamblers. Because of this high correlation, the coexistence of depression and gambling may help discriminate pathologic from non-pathologic gambling; however, the severity of depression does not correlate with the amount of money spent on gambling (Unwin, 2000). In our study, depression was the most prevalent comorbidity besides nicotine addiction. Risk factors for suicide such as major depression, substance abuse, marital breakdown, unemployment, financial crises, and legal difficulties are commonly found in populations of pathological gamblers. A study showed high rates of suicidal ideation, suicidal plans and attempts; however, no clear relationship was observed between suicidality and indices of gambling behaviour. Depression rather than gambling specific characteristics, marital difficulties, or the presence of illegal behaviours appear to be related to the risk of suicidality (Maccallum, 2003).

2.4.10 Therapeutic approaches

Pharmacological approaches

In terms of pharmacotherapy, three classes of psychotropic drugs have been used to treat adult pathological gambling - serotonin reuptake inhibitors (SSRI) like Fluvoxamine or Clomipramine, opioid antagonists like Naltrexone, and mood stabilizers

like Carbamazepine, Lithium and also some other atypical antipsychotics (Decaria 1996, Petry 1999, Hollander 2000, Pietrzak 2003, Grant 2003).

SSRI are classically used as effective antidepressants. In the recent years they have been successfully used in treating a variety of psychiatric disorders, including anxiety disorders, obsessive compulsive spectrum disorders, panic disorder, and post-traumatic stress disorder (PTSD) and pathological gambling (Irons, 2005). The pharmacological main effect of SSRI is an inhibition of the reuptake of serotonin, leading to a higher presynaptic serotonin level. This increase of serotonin is connected to a protracted decrease of serotonin-(5-HT)2A-receptors and altered sensitivity of postsynaptic 5-HT1A und 2-receptors. This pathway is largely believed to be the main underlying (delayed) antidepressant and anxiolytic effect of SSRI (Benkert und Hippius 1996). SSRI also binds to the (Opiod-) σ receptor, which has been connected to SSRI´s influence on psychosis and aggression (Naritaa, 1996). A study by Blanco evaluated the efficacy of Fluvoxamine in the treatment of pathological gamblers. Patients were treated for 6 months in a double-blind, placebo-controlled study of Fluvoxamine 200 mg/day. Outcome measures included reduction in money and time spent gambling per week. However, Fluvoxamine was not significantly different from placebo in the overall sample with the exception of male and younger patients. Fluvoxamine may be a useful treatment for certain subgroups of patients with pathological gambling (Blanco, 2002). A different study showed a better outcome of Fluvoxamine. Patients had greater than 25% decreases in their gambling behaviour scores on the pathological gambling modification and scores for gambling severity were very much improved or much improved. Fluvoxamine treatment resulted in gambling abstinence in seven of the 10 patients, suggesting it may be effective in reducing the urge to gamble (Hollander, 1998).

The first controlled trial of the efficacy of mood stabilizers in pathological gamblers showed comparable and good efficacy of Lithium and Valproate in non-bipolar pathological gamblers. Both the Lithium and the Valproate groups showed significant improvement in mean score on the Yale-Brown Obsessive Compulsive Scale modified for pathological gambling. This improvement did not significantly differ between groups. 60.9% of the patients taking Lithium and 68.4% of the patients taking Valproate were responders based on a Clinical Global Impressions-Improvement score. Findings

suggest the efficacy of both Lithium and Valproate in the treatment of pathological gamblers (Pallanti, 2002). The choice of medication should be influenced by diagnosed comorbidities and should never happen without combined psychotherapy.

Psychotherapeutical approaches

There is no standard treatment for pathological gambling. Besides pharmacological approaches, self-help groups and different forms of therapy like cognitive-behavioural treatments (CBT), and motivational enhancement therapy (MET) or imaginal desensitisation (ID) have shown therapeutical successes (McConaghy 1991, Petry 1999), (Hollander 2000, Pietrzak 2003). Regarding self-help groups, Gamblers Anonymous (GA) and its spousal component of Gam-Anon is the most popular intervention in the US with about 1,000 chapters existing. Combining professional therapy and GA participation may improve retention and abstinence. The few studies of cognitive-behavioural treatments suggest that this approach, which may include cognitive restructuring, problem solving, social skills training, and relapse prevention, is promising (Petry, 1999). Numerous studies show that cognitive-behavioural psychotherapies offer promising results in the treatment of pathologic gamblers (Hollander 2000, Toneatto 2003). Pathological gamblers were randomly allocated to desensitisation or to other behavioural procedures. ID had a specific effect additional to that of the other behavioural procedures. It is suggested the other procedures could be regarded as placebos. As the response at a mean of over five years to one week of ID is comparable with that reported to more intensive therapies, after briefer follow-up, it is suggested ID is a cost-effective therapy for pathological gambling, and is worth considering when resources are limited (McConaghy, 1991). For best results one must always treat the complete psychiatric symptom spectrum. Failure to identify and treat comorbid substance-use disorders in gamblers may lead to higher relapse rates (Maccalum, 2002).

2.4.11 Biological aspects of gambling

Focused research on pathological gambling is relatively new. Various approaches of the last years enabled to sketch a framework of abnormalities in pathological gamblers.

Neuropsychological studies indicate deficiencies in executive functions, especially decision-making functions (Cavedini, 2002), (Brand, 2005). Psychophysiological studies indicate arousal in pathological gambling to be of importance when reward is

present (Bechara, 1999). Neuroimaging studies point to abnormalities in brain functioning (Potenza, 2003). Research in neurochemistry of pathologic gamblers indicates abnormalities in different neurotransmitter systems. Genetic studies indicate the existence of specific receptor and promotor genes in pathological gamblers (Comings 1996, 1999, 2001, Perez de Castro 1997, 1999, 2002, Ibanez 2000, 2003, Eisen 2001). Results from the pathological gamblers studies fit in with recent theoretical models of addiction and pathological gambling, which stress the involvement of brain reward pathways, neurotransmitter abnormalities, the frontal cortex and the psychophysiological stress system (Goudriaan, 2004).

Imaging studies

Many studies showed that certain lesions, especially prefrontal, will cause significant impairments in gambling situations that can typically be observed in pathological gamblers. Accordingly, neuroimaging studies in pathological gamblers have focused on prefrontal areas. As pathological gamblers are believed to have an impaired impulse control, a study by Potenza focused on neural correlates of impulse control which is believed to be the vmPCF. Potenza used a Stroop paradigm to test attention and response inhibition in male pathological gamblers and a control group. FMRI was used to examine vmPCF-function during Stroop performance. Both groups demonstrated similar activity changes in multiple brain regions, including activation of the Dorsal ACC and Dorsolateral Frontal Cortex. Pathological gamblers share many neural correlates of Stroop task performance with healthy subjects but show decreased activity in the left vmPFC, an area that is implicated in disorders characterised by poor impulse control (Potenza, 2003).

A study of the same author revealed decreased activity in various brain regions of pathologic gamblers to normal controls when passively viewing gambling scenarios. For a control visual stimulation, happy and sad video scenes were used as non-gambling cues. Here pathologic gamblers displayed relatively lower activity in the Frontal and Orbitofrontal Cortex, Caudate/Basal ganglia, and the Thalamus compared with controls. Distinct patterns of regional brain activity were observed in specific temporal epochs of videotape viewing. For example, differences localised to the Ventral ACC during the final period of gambling videotape viewing, corresponding to the presentation of the most provocative gambling stimuli. Although group differences in brain activity were

also observed during viewing of the non-gambling scenarios, they were distinct from those corresponding to the gambling scenarios. In men with pathological gambling, gambling cue presentation elicits gambling urges and leads to a temporally dynamic pattern of brain activity changes in Frontal, Paralimbic, and Limbic brain structures. When viewing gambling cues, pathological gamblers demonstrate relatively decreased activity in brain regions implicated in impulse regulation compared with controls (Potenza, 2003).

Biochemical aspects

Studies on the chemo-architecture in reward processing of pathological gamblers analyse neurotransmitter genes, reactions to specific pharmaceuticals and actual transmitter concentrations. However, studies analysing direct transmitter concentrations in pathological gamblers are rare. Roy analysed norepinephrine, monoamine metabolites, and peptides of pathological gamblers in cerebrospinal fluid (CSF), plasma and urine. Pathological gamblers had significantly higher CSF levels of 3-methoxy-4-hydroxyphenylglycol as well as significantly greater urinary outputs of norepinephrine than controls, suggesting disturbances of the noradrenergic system. This system has been postulated to underlie sensation-seeking behaviours, aspects of which are thought to be abnormal among pathological gamblers (Roy, 1988). Interestingly, some clinical cases were reported in which Parkinson medication caused sudden onsets of pathological gambling, giving strong hints that dopaminergic transmission is involved in pathological gambling. Two cases are described, where increases in dopaminergic therapy were initiated by the patients. Shortly afterwards, both cases also met clinical criteria for pathological gambling. To date 29 cases of pathological gambling in patients with Parkinson's disease have been reported. This form of gambling is triggered by excessive dopaminergic drugs and does not respond to standard therapy for pathological gambling but to an adjustment of Parkinson's disease therapy (Driver-Dunckley, 2003). The effect of external dopamine on the OFC and its behaviour in response to fluctuations in reward contingencies may be a crucial pathway that explains the strong influence of Parkinson's disease medication on pathological gambling (Poletti, 2010)

Genetic aspects

Familial factors have been observed in clinical studies of pathological gamblers, and twin studies have demonstrated a genetic influence contributing to the development of

pathological gambling. Associations have been reported between pathological gamblers and allele variants of polymorphisms at dopamine receptor genes, the serotonin transporter gene and MAO-A gene. Current findings on genetics of pathological gamblers suggest liability to pathological gambling is in part mediated by genetic factors (Ibanez, 2003).

Genotyping of pathological gamblers and controls included polymorphisms at genes relating to dopamine, serotonin, norepinephrine and GABA neurotransmission. Multivariate regression analysis was used with the presence or absence of pathological gambling as the dependent variable, and the 31 coded genes as the independent variables. 15 genes were included in the regression equation. The most significant were the DRD 2, DRD 4, DAT 1, TPH, ADRA2C, NMDA1 and PS1 genes. Dopamine, serotonin, and norepinephrine genes contributed approximately equally to the risk for pathological gambling. This indicates that genes influencing a range of brain functions play an additive role as risk factors for pathological gambling. Multi-gene profiles in specific individuals may be of assistance in choosing the appropriate treatment (Comings, 2001).

Regarding genetic DRD 2 variants, Comings compared gamblers to controls, severe gamblers to light gamblers, and comorbid gamblers to isolated gamblers in respect of their frequency a taq1 variant of DRD 2. The Taq A1 variant of DRD 2 gene has been associated with drug addiction, some forms of severe alcoholism, and other impulsive, addictive behaviours. Of the pathological gamblers 50.9% carried the D2A1 allele versus 25.9% of controls screened to exclude drug and alcohol abuse. For the gamblers who filled out the questionnaires, 63.8% of them that scored in the upper half of the pathological gambling score (more severe) carried the D2A1 allele, compared to 40.9% in the lower half (less severe). Of those who had no comorbid substance abuse, 44.1% carried the D2A1 allele, compared to 60.5% of those who had comorbid substance abuse. Controls with a score of zero, 17.8% carried the D2A1 allele. These results suggest that genetic variants at the DRD2 gene play a role in pathological gambling (Comings, 1996).

A Spanish sample consisting of pathological gamblers and controls was screened for a functional DNA polymorphism in the locus of the DRD 4 gene. Results are consistent

with the existence of a significant association between genetic variants at a DRD4 gene polymorphism and pathological gambling. This association seems to be sex-influenced, since there was no significant association when only males were considered, but there was a more significant association if we only considered female subjects. Individuals with the longest allele (D7) were the most frequent in affected females (Perez de Castro, 1997). Another study was conducted to detect a possible association of MAO-A and/or MAO-B genes, but no association was found between the MAO-B polymorphic marker and pathological gambling (Ibanez, 2000).

3. Methods

3.1 Magnetic resonance imaging physics

Since the 1970s magnetic resonance imaging (MRI) has developed into both an important clinical-diagnostic and research tool. Paul Lauterbur and Peter Mansfield are two pioneers in discovering the foundations for medical and scientific magnetic resonance imaging, only recently honoured in 2003 with the noble price. The underlying mechanisms are based on quantum mechanics and thus not fully comprehensible with macroscopic logic. Here we give a basic introduction to MR-physics.

3.1.1 Spins

MRI uses the nuclear spin of nucleons, for example hydrogen protons. The spin compares partially to an angular momentum of an object like a spinning earth or soccer ball, but a quantum mechanic spin implicates some differences to spinning objects. The magnetic spin is constant, only its orientation in space can change. The spin is related to the magnetic momentum of the proton. MRI commonly uses the collective behaviour of hydrogen protons. Every spin and its magnetism has a direction (similar to the north and south pole to a magnet) and is defined as a vector. So every spin can be represented as a certain vector.

If a nucleus of an atom shows a net (= sum) magnetisation or not depends on the spin of its protons and neutrons. Odd numbers of neutrons and/ or protons form nuclei that have a net magnetisation (like 1 H, 13 C, 23 Na) and thus are useful in MRI. If the number of both neutrons and protons is even, the spin vectors of the individual components add up to a net magnetisation of zero. A given volume element of material (called voxel) contains H-Protons in a random orientation (thus neutral in sum) as long as they are not exposed to a magnetic field. Exposing this voxel to a magnetic field causes the magnetic moment vectors to orient themselves. The spins can be grouped in those which have a rather parallel or anti-parallel orientation with respect to the magnetic field. This orientation is called “Spin-up” or “Spin down”, representing a lower and higher state of energy. The number of spin-up vectors and spin down vectors is not equal, with a small excess of spin-up vectors, adding up to a bigger sum-vector in upper direction, causing a net magnetisation of the material (M) in z direction.

The majority of lower-energy Spin-up vectors per volume grow with proton-density, strength of applied magnetic field and decreasing temperature. At 36°C and 1 Tesla (20,000 times the force of the magnetic field of earth) the excess of upper spins is 0.00006 % (=6 PPM).

The spinning magnetic momentum of protons has another feature that is fundamental in MRI: Their spin-axis rotates around the direction of the magnetic field at a constant angle, called spin-precession.

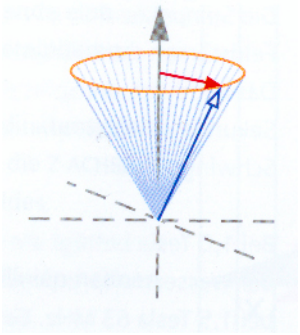


Fig. 8: The circling (=precessing) of a single "spin-up" proton in x-y direction (red), pointing up in z-direction (blue).

It can only precess parallel or anti-parallel to the applied magnetic field. In MRI we observing **collective** spin vectors (M) rather than the individual spins; the sum-vector can be changed in various angles to the direction of applied magnetic fields. The speed of the spin circles around the magnetic field is called Larmour-Frequency (w). It depends on the type of nuclei and is correlated linearly to the applied magnetic field. Its correlation to the magnetic field is expressed as

$$w = \mu \times B$$

(Omega = precession-speed, μ = the gyromagnetic factor, B = magnetic field strength). Protons of water have a gyromagnetic factor of 42,534,200 Hz/T. In a 1,5 T field the resonance frequency is roughly 64 Mhz. In the magnetic field of the earth it is 2000Hz. Since they all spin in a different phase (compensating each other) they do not cause a net magnetisation (M) in x-y direction. Thus, the dephased spins only cause M in z direction by the excess of a few spin-**up** vectors.

3.1.2 The radio frequency pulse and the signal

We can now use a high frequency pulse (RF) to change the up or down direction of the spins (z-direction) and their phases (x-y-direction). The RF pulse must have the same

frequency as the circling spins (= Larmour frequency) in order to influence the precession. The RF pulse changes the *individual* angle of the spins discretely (up or down) making a certain quantity of spin-ups to flip down. This reduces excess spin-ups and changes M in z direction.

A 90° RF will reduce the excess number of spin-ups until spin-ups and downs are equal, eliminating M in z-direction completely. At the same time it **synchronises** the precession of all protons in x-y direction, putting all spins in phase and thus changing M about 90° into x-y-direction. This is defined as application of a "flip-angle" of 90 °. A 180° RF pulse will further reduce the excess number of spin-ups until an excess number of spin-downs exist. That will turn M into adverse direction of the z-vector (from up to down). This is defined as application of a "flip-angle" of 180°.

After the RF pulse was applied, a coil can receive a signal from a group of precessing spins when in they are phase. The circling net magnetisation M induces a sinus-shaped current in a coil nearby when "approaching and leaving" the coil. This is the signal. To do so, the receiver has to be adjusted to the Larmour-Frequency. This signal is called free induction decay (FID) and is the emitted signal after a pulse was given in the absence of any gradient. It is an oscillatory resonance frequency in the MHz range.

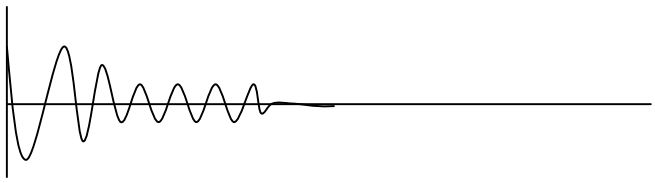


Fig. 9: A sinus curve current induced by M of spins in phase, fading as the spins dephase over time (FID) (x=time)

As the applied magnetic field of the scanner is known, the coils can be adjusted to that and match the Larmour-Frequency of the scanned matter.

T1: The "90° state" returns quickly and exponentially back into z-direction to a lower (= stable) energy-state. The absorbed energy is returned as the MR signal, but also as heat to the lattice. This is process is called T1-relaxation, longitudinal or spin-lattice relaxation. The value T1 is the time from initial excitation until 63,2% of the original M in z-direction is recovered. T1 differs from tissue to tissue, as protons behave differently

depending on their surrounding. Spins in protons of fat “rebuild” faster in z-direction (240ms at 1T) than those in liquor (2500ms at 1T). Protons in fat can give its extra-energy faster to the surrounding than protons in watery surrounding. Their relaxation time differs, and that is the reason a MRI picture can show and contrast different tissues. T1 depends on the applied magnetic field.

T2/T2*: At the same time the common phase (that all spins were circling in) decays. The spins among each other influence their precession in a randomly matter. This causes them to dephase, with M decaying in x-y-direction exponentially. This process is called T2. It is also called transverse or spin-spin-relaxation. The value T2 is the time after excitation when the signal amplitude has been reduced to 36,8 % of its origin value. The actual measured T2 is shorter than expected. This is caused by inhomogenities in the static applied magnetic field and inhomogenities of the object inside this field such as tissue-borders. These inhomogenities accelerate the ongoing dephasing. The resulting measured T2 signal decay is caused by fixed and random effects. In their sum, the resulting decay phase is referred to as T2*. T2* is much shorter than T2 and is too short to be used without techniques prolonging the signal. T2* is also tissue specific, spins in fat dephase faster than they in dephase than water. However, T2 does not depend on the applied magnetic field. M in z-direction does not recover linearly as M in x-y-direction decays. The transverse magnetisation decays faster than the longitudinal - magnetisation.

While there is nothing we can do to prevent the signal decay caused by random spin-spin interactions (T2), it is possible to compensate for the fixed magnetic inhomogenities that cause additional dephasing (T2*). After the initial 90° RF pulse a FID is emitted and the spins start to dephase. Now a 180° RF *reverses* the dephasing and the spins start to re-phase again. The transient moment they come into phase again, they emit another signal, called the Spin-echo. This can be imagined as runners of different speed starting from the same point to which they will cross again together when their direction is turned around at 180° simultaneously. The necessary time for re-phasing is called echo-time (TE). This process can be done as many times as the fixed T2 decay last. This enables multiple echo signals within the time frame of T2, thus increasing given information. To receive an echo-signal at 30 ms, the 180° RF pulse is given 15 ms after the 90° pulse.

3.1.3 From a signal to the picture

In order to receive a signal that uniquely codes for a specific voxel to construct a picture, gradients are applied to the static magnetic field for spatial encoding. They are generated by coils of wire located within the bore of the magnet through which current is passed. The passage of current through a gradient coil induces a gradient (magnetic) field around it that either subtracts from or adds to it. Gradient strength is described as mT/m (common is 10-20 mT/m). Higher field strength leads to better outcome. There are 3 gradient directions possible: a z-gradient for transverse selection, an x-gradient for axial selection and a y-gradient for coronar selection. The coils surround the patient, making it possible to have a selection in each direction. If the RF-pulse of the gradient is tuned to a certain precession frequency only the protons with this same frequency will absorb this energy. This means only the protons in which one is interested are excited. Therefore the first gradient is the slice selection gradient. This gradient will give the protons of the body-part slice of interest the right precession frequency. The other parts of the body precess at the "non-excited" frequency. The original magnetic field of the scanner of 1,5 T is rising e.g. from 1,4 T to 1,6 T by the gradient. The protons in that magnetic field are now precessing from 60 to 68 MHz and can be activated by a specific RF-pulse. This can be a very narrow bandwidth RF-pulse (only the 64 MHz protons will be excited), or a wider range to make a slice thicker. Slice-thickness can also be changed by gradients steepness. A steep gradient will make the 1,5 T range much smaller (the slice thin). In this way slice location and thickness are defined. To compensate the dephasing, the slice select gradient is switched twice (during 180° pulse). Only the selected protons will dephase again and they are in phase again. In a transverse slice, all protons have the same direction. To enable spatial decoding, a second gradient is switched on (the **frequency encoding gradient**). Each column now gets an own frequency (Hz). This encoding is given twice; once before the 180° pulse to dephase the protons and once during echo sampling (readout).

A chosen slice could be a 256^2 matrix picture. During echo the frequency encoding gradient is on and 256 different frequency-columns are made. Each column has a different frequency. The steepness of this gradient is set by the FOV (field of view) parameters. With a steep frequency encoding gradient there is a large frequency difference between two points. The results are smaller pixels with large spatial

resolution. The echo-signal however, is smaller because the protons are less in phase. A shallow gradient would give high signal. Now each voxel in a certain column (all with the unique frequency) must have one extra code because in one column all protons have the same frequency (there were 256 columns). This is done by the phase-encoding gradient which will give each voxel in one column a unique phase. This gradient is switched on 256 times in between the 90° and 180° pulse. Now each voxel has a unique code. This phase encoding gradient is switched between two pulses and there is always

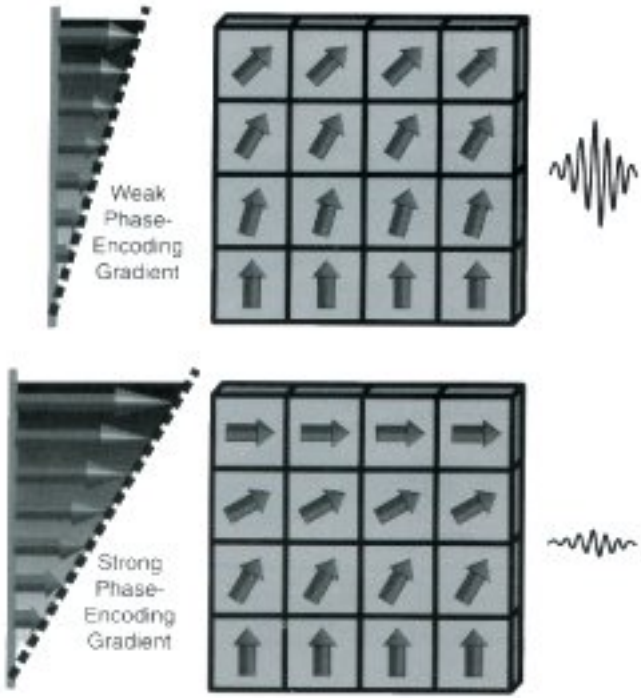


Fig. 10: Compromising between week and steep gradient application

some time between this encoding and the read-out of the signal (the echo). In weak gradients, less dephasing causes strong echoes. In the other situation we receive a smaller echo-signal, because of the strong dephasing. The spatial resolution however is better.

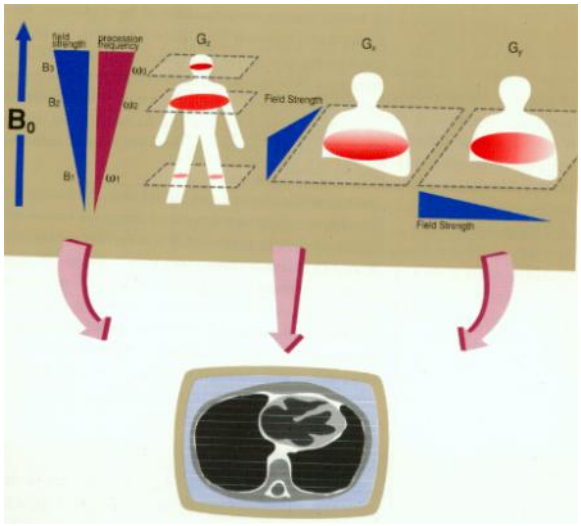


Fig. 11: A combination of all gradients enables 3D spatial decoding

Figure 11 shows all 3 gradients together. First the slice selection then left-right frequency encoding and at last a phase encoding gradient. Frequency and phase direction can be changed. Finally all the measured frequencies build up the K-room. Every point of the K room contains information of the whole picture. The centre parts of the K-room contain information regarding structure and contrast; peripheral parts contain information about resolution and borders. An analysis of the spectrums (Fourier transformation) of the K room is decodes them into an actual picture as we know it.

3.1.4 Scanning parameters

Our study was executed with a 3 T Siemens Trio MRI Scanner. We used a echo-planar-imaging (EPI) T2* sensitive pulse sequence. Each scan protocol included 38 axial slices, each 2mm thick with 1 mm gap; a TR (scanning time of a whole volume) of 2.2 seconds, a TE of 25ms, a flip angel of 90°, a field-of-view (FOV) of 192 x 192 mm² with a 64 x 64 matrix. Thin slices reduced susceptibility related signal drop-out in the vicinity of the Ventral Striatum and the VMPFC.

3.2 Functional MRI and the BOLD signal

Functional magnetic resonance imaging (fMRI) reflects a complex relationship between the MRI sequence design and the physical, chemical and physiologic nature of the tissue. FMRI images are formed from the signal differences between activated and not activated image acquisition. The basic mechanism for these signal differences is most often attributed to the diffusion of water in local inhomogeneous magnetic fields caused

by susceptibility differences between tissues. These local inhomogeneous fields can be caused be exogenous (e.g. Gd-DTPA) or endogenous (desoxyhaemoglobin) contrast agents. It is necessary to have an understanding of cerebral blood circulation and its regulation as well as the physics underlying fMRI signals to grasp the complex interplay between each.

3.2.1 Cerebral circulation

There are unique features of cerebral blood circulation, the blood-brain barrier being one characteristic. The blood-brain barrier helps to isolate and protect the brain from ionic changes and other stimuli. Larger arteries account for a relatively greater portion of vascular resistance in the brain than in other vascular beds. In addition, the cerebral vessels are subject to a tight auto-regulatory process, which makes them responsive to changes in arterial pressure, chemical stimuli, hypercapnic acidosis and hypoxia. The microvasculature is formed by successive branching to the capillary level, which leads to a tremendous increase of surface area for tissue exchange. The diameter of precapillary arteriole segments determines the rate of blood flow through the capillaries. At this point, the main contribution to vascular resistance is made. The structure of the microcirculation is tissue specific and varies with regional specialisation of function.

Local metabolic demands or patterns of growth determine the amount of blood flow to that tissue as well as inter-capillary distances. The fraction of blood in tissue provides an approximate estimate of capillary density and, to some extent, the metabolic rate (Bassingthwaighthe, 1990). Consequently there is a marked variability in the complexity of micro-vascular structure. Therefore, parameters used in fMRI modelling studies should be considered as approximate. In contrast to the parallel, evenly spaced capillaries in heart and skeletal muscle beds, cerebral capillaries are tortuous and can be assumed to be distributed randomly.

The cellular components of blood include red blood cells (RBC), white blood cells and platelets. Haemoglobin (Hb) contained within the RBC can exist in the deoxygenated state (desoxyhaemoglobin) and oxygenated state (oxyhaemoglobin). Oxygen is carried by Hb to the tissues to satisfy the metabolic demand. FMRI modelling assumes RBCs to be spherical. This is only an approximation as they are biconcave discs and also undergo a deformation during transport in smaller capillaries.

3.2.2 Flow regulation and neural control

Neural activity is associated with an increase in metabolic activity and blood flow. The exact mechanism by which this occurs remains unclear. The substances responsible for mediating the link between neural activity and blood flow are still under investigation. There is evidence implicating carbon dioxide, pH, potassium ion, tissue osmolity and adenosine. These metabolic products in conjunction with other regional regulators may act through local arteriolar endothelium-dependant vasoactive substances, such as nitric oxide. It is not known how the effect of local metabolic products is propagated to the regulatory regions upstream of exchange sites. There appears to be no control in the postcapillary venules that is metabolically mediated. Control of venous vessels in the brain is thought to be under nervous control. The resting distribution of cerebral blood flow is rapidly altered by changes in activity of different cortical regions. Hand motion has been demonstrated to result in a corresponding 50% - 100% increase in local cerebral blood flow in cortical sensimotor regions (Olesen, 1971). The local increase in cerebral blood flow is associated with increased oxygen uptake and only a slight increase in pO2 (Lassen, 1978). Oxygen is unlikely to be the primary local control because the percentage rise in cerebral blood flow exceeds local metabolic demand. Specifically, metabolic uncoupling between local blood flow and oxygen demand was supported by a 25% increase in cerebral blood flow, a 5% increase in oxygen utilisation, and a 19% decrease in oxygen extraction fraction. The decrease in oxygen extraction fraction corresponds to an increase in local pO2 and oxyhaemoglobin.

3.2.3 The BOLD-signal

FMRI studies of the brain can presently detect activation of neurones using three methods: 1. Dynamic susceptibility contrast (DSC) MRI, blood oxygen level dependant contrast (BOLD) MRI and spin tagging MRI. As we only use the BOLD technique, only this one will be explained. Knowledge of the paramagnetic nature of deoxyhaemoglobin and its effects on MRI signal long proceeded the clinical development of magnetic resonance (Pauling, 1936), (Brooks, 1975). The heme iron of deoxyhaemoglobin is in the high spin ferrous (Fe2+) state with four unpaired electrons in the outer shell. This state has a large magnetic moment and gives deoxyhaemoglobin paramagnetic properties similar to gadolinium chelates. In contrast, the heme iron in oxyhemoglobin transfers one of the electrons to the oxygen molecule, changing the

heme iron to a low spin state with no net magnetic moment and thus making oxyhemoglobin diamagnetic.

Deoxyhaemoglobin has little effect on direct T1 relaxation of water protons because the four unpaired electrons of the iron are sequestered within the deoxyhaemoglobin molecule. Deoxyhaemoglobin does have a significant bulk T2* susceptibility effects. When an external magnetic field is applied, the paramagnetic ions align with the field, resulting in a relatively large local field. In contrast to exogenous paramagnetic contrast agents that are given intravenously and localise to the plasma compartment, deoxyhaemoglobin is located to the intracellular space of RBCs and causes them to have a different susceptibility than the surrounding tissue and plasma. The susceptibility difference between paramagnetic deoxyhaemoglobin inside the RBCs and the surrounding tissue leads to a locally inhomogeneous magnetic environment.

As mentioned in the previous chapter, protons moving in the locally inhomogeneous magnetic environment experience different field strength, which in turn, affects their transverse relaxation. Thus protons precess at different frequencies, loosing phase coherence. There is a resultant loss of signal in the region. Signal loss from paramagnetic deoxyhaemoglobin is more apparent with a longer TE, which allows more time for protons to lose phase coherence. The relationship between susceptibility and blood oxygenation is linear. The T2* relaxation rate of blood solutions is directly related to the level of oxygen saturation of haemoglobin as well. The contribution of field inhomogeneity to signal decay depends on the strength of the applied field. The T2* relaxation rate of blood increases as a quadratic function of field strength. At high fields and high resolution, the image effects of paramagnetic blood are particularly apparent. Aside from oxygenation differences, signal loss as a result of magnetic susceptibility is apparent at tissue interfaces where there is a significant difference between tissue susceptibilities. Bone-air interfaces as are found at the skull base can result can result in severe signal loss and image distortion. Due to its non-invasive nature, the BOLD technique is a very well applicable technique. Changes in oxygenation of endogenous Hb and the resultant effects on signal intensity provide the basis for observing changes in local blood flow and thus neural activation. This effect was first described in rodents at extremely high field strength (7 T and 8.4 T) and with

high resolution and was termed blood oxygen level-dependent contrast (BOLD) (Ogawa, 1990).

3.2.4 Time course of activation

FMRI studies show that signal changes are observable within seconds after the onset of stimulation. The latency of activation seen with the BOLD effect in primary cortical regions is approximately 5 to 8 seconds from stimulus onset to 90% maximum and 5 to 9 seconds from stimulus cessation to 10% baseline (Kwong 1992, DeYoe 1992), (Blamire, 1992). A transient undershoot at the end of stimulation is observed and a decrease in baseline can be seen after the first activation period during cycling activation (Frahm, 1992). This rise time may represent the vascular transit times of tissue (Kwong, 1992). The T2* signal change induced by neural activation in not expected to be detected until the blood has passed through the capillary bed and relatively unoxygenated blood fills the venous capacitance vessels. The observed signal rise times of approximately 4 seconds are in good agreement with the cerebrovascular transit times measured with 15-oxygen labelled carboxyhaemoglobin (Grubb, 1974).

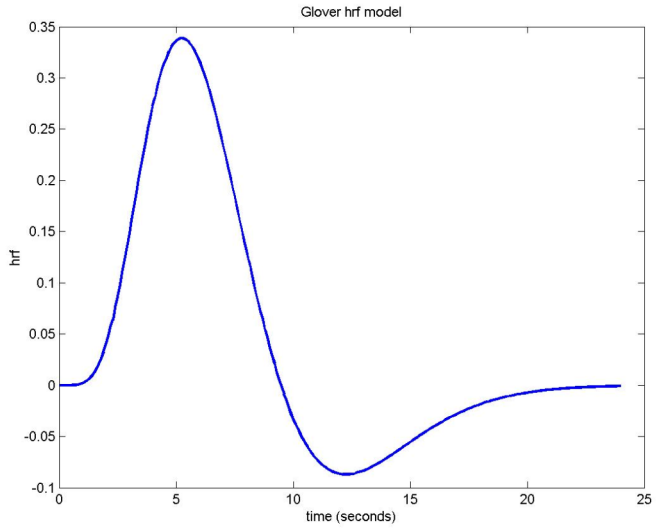


Fig. 12: A canonical hemodynamic response function (x= Time in seconds, y= blood flow change)

Animal studies have shown that signal changes could be visualised within seconds of lowering blood oxygen levels by administrating different percentages of inhaled oxygen (Turner, 1991). A similar 6-second rise time was seen as well as a distinct overshoot when oxygen levels were restored. The authors postulate the overshoot could indicate a transient decoupling between blood flow and oxygen utilisation during the first minute of restored oxygen levels. Limitations lay in the time course of physiologic response

that occurs several orders of magnitude slower than actual neural responses observed electrophysiologic techniques, such as EEG or MEG. Therefore fMRI is appropriate for localisation of sustained activation of distinct populations of activated neurones, but may be less appropriate for investigating the dynamics of interactions between populations.

3.3 The experiment

3.3.1 General aspects

To analyse imaging data, an experiment must allow specifying at what time which experimental condition was present. There must be a clear definition of **which conditions of interest** is present **at what time**. Different conditions are represented as regressors of "stimulus-onset-times" and enter a mathematical framework that is a model to explain the measured imaging data. Condition timing can vary, resulting in either block design or event related design. Additionally, the "intensity" of a condition (e.g. loudness, brightness) can be modulated as a parametric modulation design.

In a **block design** a condition is active for a longer period (more than 1000ms) and intermediately inactive, e.g. a light on a screen being on for a minute and off again. The presence or absence of these conditions over time can be represented numerically with 1 or 0. Searching brain regions that react to the light on the screen, one can use this function as a model of how a certain region (i.e. visual cortex) of the brain should react to light. To use this activation pattern as a model for blood-flow related cerebral activity, we adjust it to a physiologic correlate of hemodynamic activity. In SPM 2 regressors can be convolved with the hemodynamic response function (standard hrf function of the BOLD-effect). The altered regressor represents a biologic activation pattern and can be used for regression analysis.

In an **event related design**, conditions are represented shorter and usually in a randomised pattern. We only use the onset of these conditions to form a model of cerebral activity. A simple experiment would be a light on a screen that flashes for 50ms in a randomised pattern (jittered timing). Fig. 13 shows stick functions for each condition onset and its convolution with a hrf-function (Fig.14).

Fig. 13: Stick functions: "Light on"-regressor, (x=time)

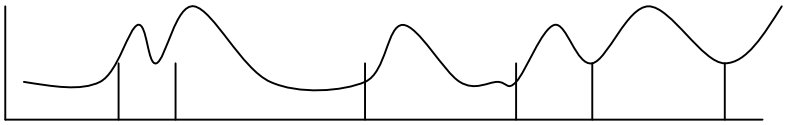


Fig. 14: A convolved function (stick functions and hemodynamic response function), (x=time)

To analyse how well the model regressors explain the measured data, they enter into the common mathematical framework (General Linear Model). This model is described in its own chapter.

3.3.2 Programming and implementation of an fMRI experiment

FMRI experiments demand a complexity of technical appliances and their co-ordination. Figure 15 shows the central role of the individually programmed routine that presents stimuli at a precise time, triggers various output devices (e.g. projector), records subjects response data (e.g. button presses) and produces log-files. All relevant behavioural data, especially the timing of conditions is extracted from these log-files. The presentation program also records the MRI scanner for synchronised action.

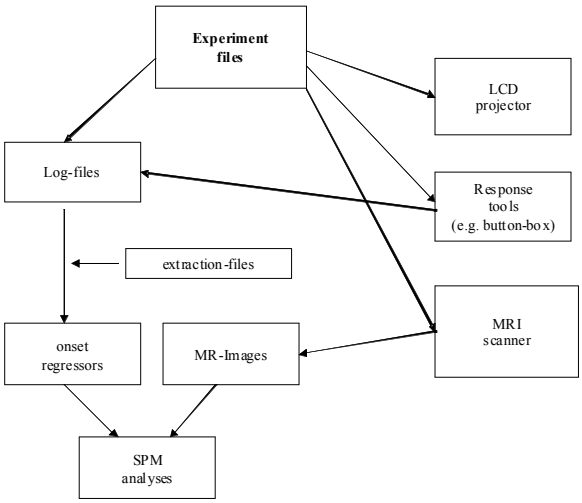


Fig. 15: Technical set-up of an fMRI experiment as used in the current thesis

For these purposes we use “Presentation 0.52™” software (http://nbs.neuro-bs.com). “Presentation™” uses three levels of programming, a Graphical User Interface (to coordinate the experiment and all interacting devices), a presentation-file (to control execution of experiment) and a scenario-file (to define and provide stimuli material).

3.3.3 The gambling task

Our goal of the experiment was to provide a real gambling situation. For this reason we programmed a simple card game in which a subject can gain or lose money, when guessing correctly which of two hidden cards the red one is.

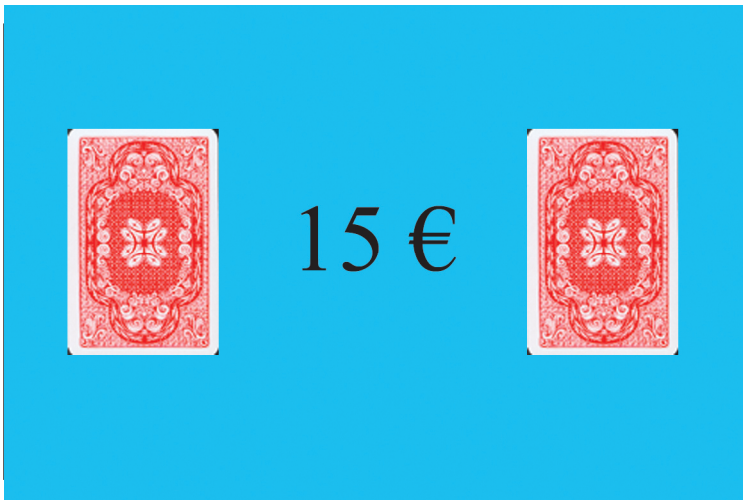


Fig. 16: A screenshot from the gambling paradigm of the current thesis

An LCD projector projected the stimuli on a screen positioned within the bore of the magnet which was viewed by the subject through a mirror (10 x 15° field of view) positioned on the head coil. The game consisted of 3 sessions each having 79 trials, representing 237 gambling situations in total. A trial took 4 seconds. First, 2 seconds of watching the card backs and making a guess (which the red one is) by pressing one of two buttons of a button box. After 2 seconds the chosen card is turned around and one Euro is added or subtracted to a constantly shown account of money. The “revealing” was defined as stimulus onset (of winning or losing). There were additional 2 seconds of waiting after each card representation. We programmed this paradigm so that the volunteers had the impression of a real gambling situation. To enable this pseudo-choice situation, programming included a reaction to the individual button: If a trial was destined to be won, the red card was placed to the right side upon a right button press and to the left side upon a left button press. That fact combines a feeling of choice for the participants within a standard and comparative train of events.

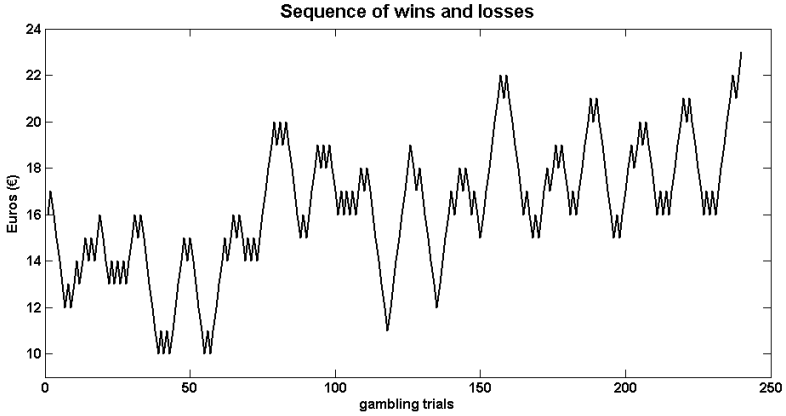


Fig. 17: The fixed train of winning and losing in 237 gambling trials

This was programmed in Matlab™ using a noisy sinus wave with a positive linear trend and imported into the Presentation™ software. For analysis, an extract file (written in Matlab™) was used to extract the timing of these onsets from the individual logfile.

SPM 2 does not use the time of stimulus onset in absolute time, but in scans. Since each scan has a defined duration, the stimulus onsets can be converted from TRs into milliseconds. The TR should never be in a fixed ratio to a stimulus onset pattern to prevent confounding scanning patterns with experimental conditions.

3.4 Image processing and statistical analysis

3.4.1 General aspects

In functional neuroimaging we relate imaging data to a model that tries to predict the measured data. The model may include various other data like behavioural or demographic data. Functional neuroimaging, as the name suggests, is used to show functional aspects of the brain, such as a change of cerebral blood flow in fMRI, a change of receptor availability in PET or a change in electric nervous potentials in EEG. In this study we relate voxelwise T2* magnetic resonance signal intensity data over time to a model of regressors representing cerebral activity of conditions of a gambling task.

3.4.2 Statistical parametric mapping

One approach to statistical analysis of functional MRI data is realised in Statistical Parametric Mapping (SPM2), a program developed by Karl Friston et al. at the Functional Imaging Laboratory, London, UK (http://www.fil.ion.ucl.uk/spm). It is

generally used to identify functionally specialised brain responses and is the most prevalent approach to characterise functional anatomy and disease related changes. SPM is a voxel based approach (thus mass-univariate), employing classical inference (F & T-tests) to make comments about regionally specific responses to experimental factors. SPM analyses each and every voxel using any standard univariate test. The resulting statistical parameters are assembled into an image, the Statistical Parametric Map. These maps are interpreted as spatially extended statistical processes by referring to the probabilistic behaviour of Gaussian random fields (GRF) (Adler 1981, Worsley 1992, 1996, Friston 1994). GRF model both, the univariate probabilistic characteristic of a statistical parametric map and non-stationary spatial covariance structure. SPM uses the General Linear Model to analyse and make classical inferences about spatially extended data through statistical parametrical maps. It also uses the GRF to resolve the multiple comparison problem that arises from making inferences from a volume of a brain consisting over thousand s of voxels and their thousands of T- or F-tests. The analysis of functional neuroimaging data can be broadly divided into: 1. Pre-Processing, 2. Estimating the parameters of a statistical model, 3. Making inferences about those parameter estimates with appropriate statistics.

Pre-Processing

Before imaging data is related to a model it must be pre-processed.

Goals of pre-processing are:

- Converting scanner images to analysis - software readable images
- Checking raw data for artefacts
- Interpolation of slice-wise acquired data to a "whole-brain at one moment"-scan (slice timing)
- Correcting for motion artefacts (realignment)
- Fitting individual imaging data to standardised brain templates (normalisation)
- Filtering the data in order to focus on real activation patterns instead of noise and normalise the error distribution to allow a parametric analysis (smoothing)

In order to process the images they are converted from the scanner format to a SPM/Matlab format. Each full scan volume consists of 38 slices, with 64 x 64 voxels each. We discarded the first 3 - 5 scans of each session in for scanning onset artefacts.

For artefact tracing, we used two program tools: “SPM-movie”, which shows a series of all scans that allows to detect and sort out unusual signal intensity changes. The more exact option is called “Spike-fix”, coding with colours how many standard deviations the signal differs from the mean value. Unusual signal activity changes (spikes) can be removed and replaced by an averaged signal. Our data contained no significant artefacts and no scans were replaced.

Slice timing

Analysing the brain as a whole one must correct for the fact that the brain slices are measured slice after slice. SPM relates the acquisition time of all slices (within one scan) to a reference slice, in our case to the middle slice. Mathematical transformation interpolates the scans as if the brain was scanned in a single moment.

Realignment

Next the imaging data is corrected for motion artefacts. A movement of only 1/10 of a voxel can produce a signal change of 1% - 2% inside the brain and 7% - 8% at the edges, while the BOLD contrast has a signal change of only 5%. In our study all participants showed less than 3mm total head movement for each session. However, movement correction is always necessary. We realign by calculating the change of 6 parameters (shift-transformation into x, y, z direction and rotation around those axis) of each image in comparison to the first image. The train of changing parameter can be shown in a graph that gives an estimation of how much and in which direction the subject moved. Then SPM uses these parameters to recalculate all scans with the first scan as a reference.

Normalisation

To compare different brains in a standard space, the individual brain is morphed to a standard template brain. When e.g. subject A had big ventricles and B small ones, they both have same sized ventricles after the normalisation process. The size of their ventricles is adjusted to a standard brain of the Montreal Neurological Institute (MNI).

EPI pictures are adjusted to an EPI-template, high-resolution T1 picture to a T1 template. There are different mathematical approaches to find the optimal parameter estimates that match the individual scans to a template brain; in our experiment we used a b-spline interpolation.

Smoothing

Finally we can increase the signal to noise ratio (SNR) and accentuate clustered activity. Single exclusively activated voxels do not represent real brain activity, but much rather noise. Also, sharp edges in signal patterns normally do not represent activation patterns; it is rather a "soft" edge in signal pattern to represent real neural activity patterns. Applying a Gaussian fields filter erases single voxel activation and softens activation cluster edges. Also, a normal distribution of errors is a condition of parametric analysis and applying the Gaussian fields theory in order to correct for multiple comparisons. Smoothing the data with a Gaussian fields filter increases the normalised error distribution. However, smoothing does cause a loss of wanted signal. In our study we applied a 10mm smoothing filter. That actually means that each voxel is averaged to its neighbouring voxels within a certain radius, a Gaussian curve with a width of 10mm at half maximum.

Statistical Analysis

The analysis software SPM (Statistical Parametric Mapping), that were used in the current thesis, employs the General Linear Model (GLM) and will therefore be introduced in the following. The GLM was derived from multiple regression analysis and provides a statistical framework that incorporates a number of different statistical models: t-tests and f-tests, linear regression, analysis of variance (ANOVA), analysis of covariance (ANCOVA), multivariate analysis of variance (MANOVA) and multivariate analysis of covariance (MANCOVA), (Cohen, 1968). The GLM is an equation that combines variables for the measured response with a linear combination of explanatory variables and an error term:

$$Y = x\,ß + e$$

For 2 conditions:

$$Y = X_1\,ß_1 + X_2\,ß_2 + e$$

For n conditions:

$$Y = X_1 \beta_1 + X_n \beta_n + e$$

The data comprises the GLM the vector Y of the size 1 x N (number of observations). The GLM models the data Y by the weighted sum of predictor variables or regressors and residual errors. The number and nature of regressors depend on the a priori hypothesis, namely which predictor variables (in our paradigm "winning or losing situations") are sought to influence the observed variance (in our results the grey values of a specific voxel). The regressors of a particular model comprise the design matrix X (Fig.20) that have the size N x P (N = number of observations, P= number of regressors). The residual error ε between the predicted and the actual data comprise a vector of size N x 1. The GLM uses an ordinary least square approach to define parameters or regression weights that minimize the residual errors. The parameters ß for the predictor variables are summarised in a P x 1 vector (P = number of regressors). All statistical tests are formulated in the GLM by contrast matrices that relativise the planned contrast between a variable number of parameters with respect to the residual errors of the model.

1st level and 2nd level analysis

The GLM is applied to the statistical analysis of fMRI data for each individual participant (1st level) and also for the group statistics (2nd level analysis). Both analysis processes can be divided into the model specification and model estimation. Model specification is the selection and creation of regressors, model estimation refers to the calculation of the parameter estimates of the model that lead in the lowest residual error. For the 1st level analysis, the regressors are constructed based on the knowledge about the timing of the various experimental conditions during the experiment and the time course of the canonical hemodynamic response function. The underlying assumption is that the neural event elicited by the processing of a particular stimulus during the experiment, i.e. winning/losing money in the experiment of this current theses, results via neurovascular coupling in the canonical BOLD response. The relationship between stimulus onset and expected hemodynamic response function is a convolution of a stick function (representing the very short neural event) with the canonical response function. To obtain a hypothetical hemodynamic response function for one experimental condition across the time course of the whole experiment, a stimulus onset vector containing "sticks" only when a stimulus of that condition was present, is convolved

with the hemodynamic response function. These hypothetical BOLD-responses predict for each point in time, i.e. each acquired volume of an fMRI scan, a certain level of activity. The 1st level analysis model specification includes the hypothesis driven selection of regressors that are expected to explain i.) a significant amount of the variance of brain activity during the course of an experiment and ii.) comprise the events of the different experimental conditions that are aimed to be contrasted during the subsequent statistical inference. The onsets of winning and losing events were convolved with the canonical hemodynamic response function which resulted in their specific regressors. During model estimation, the GLM uses an ordinary least square approach to define parameters that minimize the residual errors. This is followed in SPM by a "Restricted Maximum Likelihood"-algorithm that improves the validity of this estimation. After model estimation, the parameters of the regressors indicate how much the particular regressor contributes to the explanation of the variance across the time series in a particular voxel.

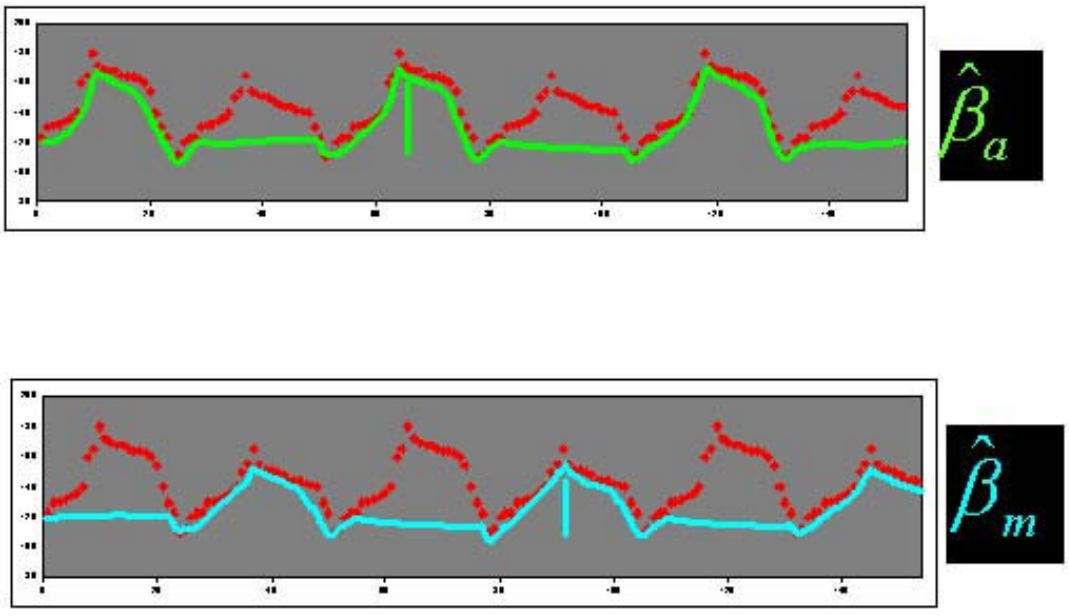


Fig. 19: Graphic visualization of two regression analyses of ß1 and ß2

In the 2nd level analysis, the parameter estimates of the various regressors are compared to infer from the effect in the sample to the population. Thus, the regressors of a 2nd level model comprise the parameters estimates of the 1st level analysis to a particular experimental condition of all subjects. The 2nd level parameter estimates correspond to the group mean of the 1st level parameter estimates of a particular regressor. The statistical test is formulated by a contrast vector that weights the 2nd level parameter

estimates in a hypothesis driven manner. The resulting statistical comparisons are computed in SPM for each voxel independently. The hypothesis tests via the GLM are made by SPM using mass- univariate approach. For each voxel, the product of a contrast vector × the parameter estimates, in other words the weighted sum of the parameter estimates is relativised with respect to the variances across subjects in that voxel. In the current thesis, the mean activity across sessions for winning and losing events for each subject were entered in the 2nd level analysis.

3.5 Participants

33 subjects participated in our study: 12 pathological gamblers, 18 healthy controls, 6 of them excluded and 3 healthy controls for pilot scans. The pathological gamblers, all right handed and smokers, were recruited from the behavioural clinic of the Department of Psychiatry and Psychotherapy, University Hospital Hamburg-Eppendorf, Germany. They were aged 37.3 ± 7.4 years (mean ± sd). All pathological gamblers played mainly slot machines, but not card games or traditional casino games. The control group consisted of 12 age matched healthy males (all right handed) and were recruited through advertisements. This group was aged 32.3 ± 5.6 years and did not statistically differ from the pathological gamblers in respect to age ($t(22) = 1.9$, p = n.s.) and smoking ($t(22) = 1.9$, p = n.s.). 6 controls were excluded due to matching reasons or not fulfilling inclusion-criteria. Inclusion-criteria were being male, being over 18 years old and not being under the influence of drugs. Every participant had to meet health standards for MRI-scanning and gave written informed consent prior to inclusion into the study. They also underwent a structured psychiatric interview (MINI) (Sheehan, 1998) performed by an experienced psychiatrist (T.R.). No active axis I disorders apart from depression in four pathological gamblers was present. Depression was further assessed using the Beck Depression Inventory (BDI) (Beck, 1961). The mean depression score was 2.5 ± 2.6 for the controls and 11.5 ± 7.5 for the pathological gamblers group. Therefore, all imaging analyses accounted for higher depression scores in the pathological gamblers group using an ANCOVA. The gamblers had been gambling for 13.4 ± 6.8 years.

All pathological gamblers had a diagnosis of pathological gambling according to DSM IV. Furthermore all individuals were assessed with a more detailed German gambling questionnaire “Kurzfragebogen zum Glücksspielverhalten” (KFG) (Petry, 1996), which is a modified version of the 20 questions developed be “gamblers anonymous” and

greatly overlaps with the questions of the South Oaks Gambling Screen (Lesieur, 1987). In a validation study including 558 pathological gamblers this instrument has shown a high consistency (Cronbach's alpha = 0.79) and a high test-retest reliability (r = 0.80) as shown by the same group in an additional sample of 44 pathological gamblers assessed over 2 weeks (Petry, 1996). This questionnaire contains 20 items on a 4 point Likert scale (0 to 3 points). The threshold for pathological gambling on this scale was set to 16 points. Gamblers scored in between 21 and 53 points (35.6 ± 9.7; mean ± sd). Controls scored between 0 and 9 points (2.9 ± 2.9; mean ± sd). Pathological gamblers and controls consumed alcohol, but did not fulfil the criteria for alcohol-abuse or alcohol-dependence according to DSM IV. Three controls had previous experience with marijuana. All participants were medication and drug free except coffee and cigarettes on the day of the scan. After scanning each participant was questioned if he had the urge to continue gambling or felt the task could lead to a relapse. Even though participants described gambling as pleasurable, no participant reported the feeling of a continuous gambling urge after playing the task. No pathologic gambler made use of our crisis intervention to prevent them from relapsing. Four healthy controls had two be excluded because of scanning problems (Nr.1, Nr. 4, Nr. 17 and Nr. 18), one healthy control because of THC intoxication (Nr.6) and one for matching the criteria of a major depression (Nr. 15). A permission to execute this study was given by the ethic board of physicians in Hamburg, Germany.

Subject	DOB	DSM-IV	KFG	BDI	MINI	Smoking	Other
Control 1	1979	0	3	1		Yes	Excluded
Control 2	1974	0	3	4		Yes	
Control 3	1966	0	3	0		Yes	
Control 4	1978	0	2	2	Alc. (4)²	No	Excluded
Control 5	1963	0	0	1	Past Hypomanic phase	Yes	
Control 6	1976	0	6	5	THC(3)²	Yes	Excluded
Control 7	1964	0	9	0		No	
Control 8	1970	0	0	2		No	
Control 9	1975	0	0	3	Alc. (3)² THC(4)²	Yes	
Control 10	1970	0	6	1	Social phobia²	No	
Control 11	1974	0	0	1		Yes	
Control 12	1969	0	5	1		No	
Control 13	1975	0	6	3	Alc(4)²	Yes	
Control 14	1970	0	2	1	Alc(3)²	Yes	
Control 15	1973	0	3	16		No	Excluded
Control 16	1975	0	2	2	Alc(3)²	No	
Control 17	1964	0	3	9	Dysthymic² THC²	No	Excluded
Control	1965	0	0	9	Depress.	Yes	Excluded

18							
PG 1	1970	8	42	20	Acute manic phase²	Yes	
PG 2	1969	7	26	6	Social Phobia², Alc²	Yes	
PG 3	1969	7	53	8	Acute manic phase, Drugs², Fear disorder	Yes	
PG 4	1976	10	43	5	Suic.attem.*	Yes	
PG 5	1966	8	40	26	Major depress., Fear Disorder	Yes	
PG 6	1955	10	28	31	Major depress.	Yes	
PG 7	1963	8	30	7		Yes	
PG 8	1973	8	42	6		Yes	
PG 9	1965	7	41	18	Suicidal*	Yes	
PG 10	1955	6	25	6		Yes	
PG 11	1973	6	21	10		Yes	
PG 12	1955	7	26	5		Yes	

Table 4: Results of healthy controls and pathologic gamblers

*= patient was not acute suicidal and was in therapeutic treatment.

²= control/gambler did not reach enough points in MINI test for diagnosis of mentioned disorder, but did score in this section.

4. Results

4.1 The design matrix

A framework of all variables of interest and error: forming the model (to which we fit the measured data according to the general linear model).

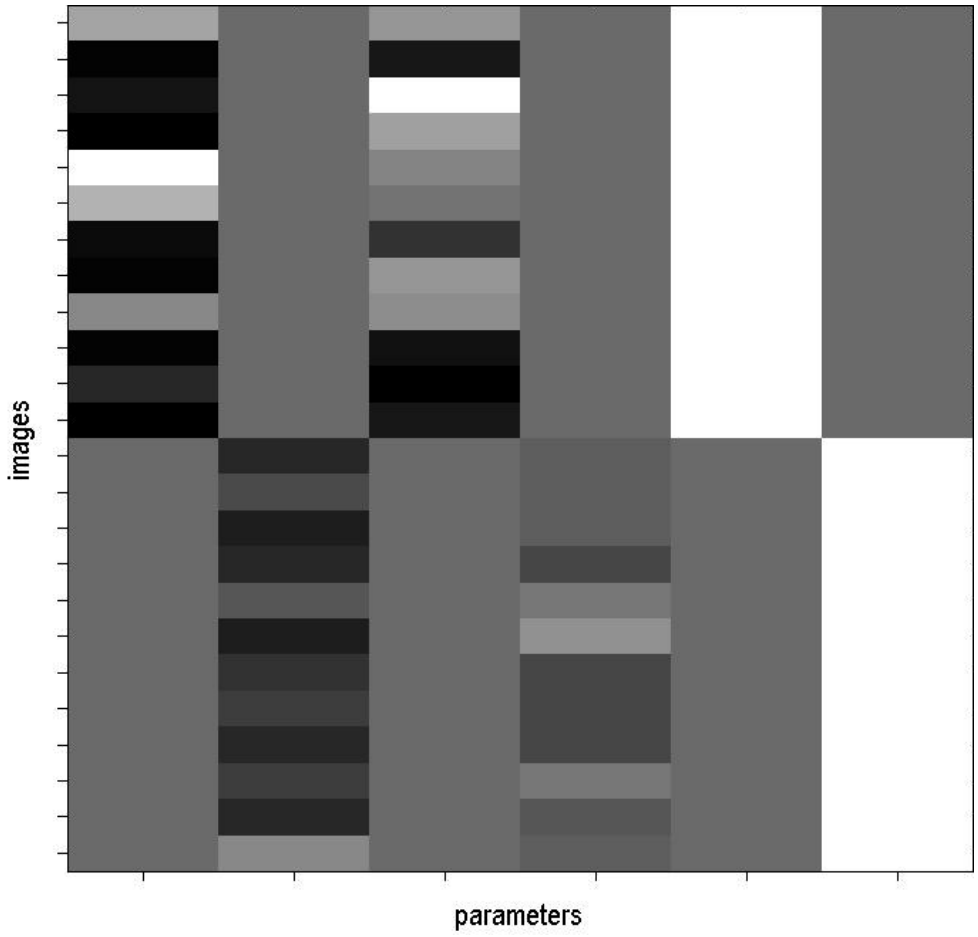


Fig. 20: A 2nd level statistic design matrix x=parameters [winning and losing] and y=images [controls and gamblers]

4.2 The gambling-task activates the human reward system

According to our a priori hypothesis we find reward related activity in the Nacc of all participants and in the PFC only in healthy men.

Testing for global results of reward

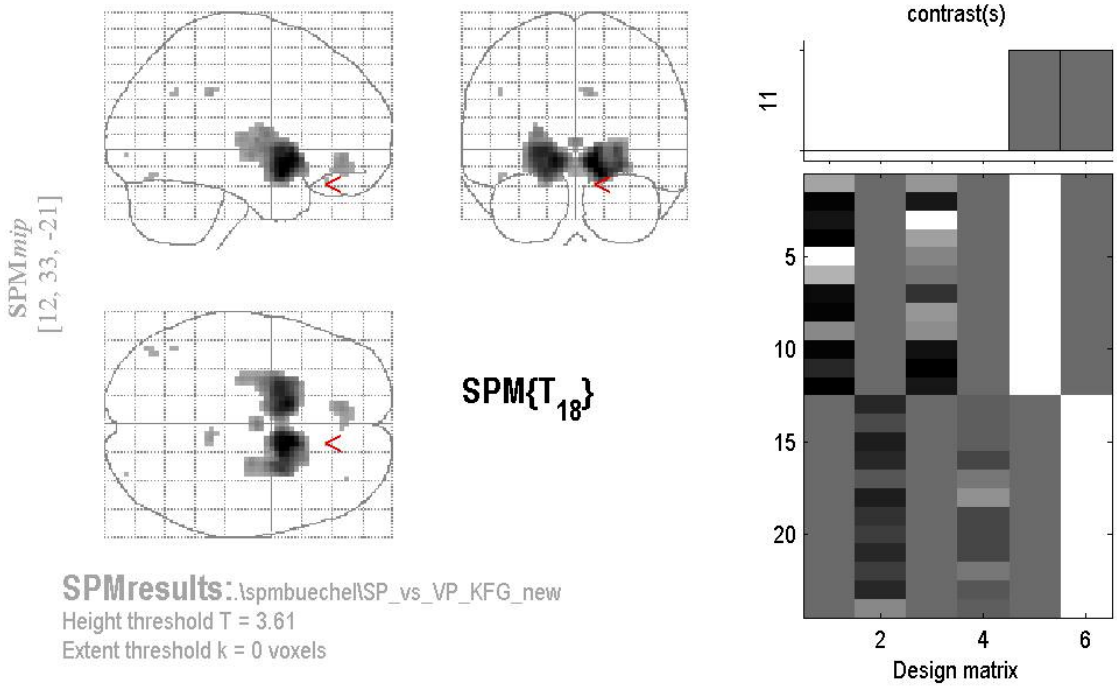
According to our a priori hypothesis we find reward related activity in the Nacc of all participants and in the PFC only in healthy men. As we focus on reward related activity, we only use a specific contrast from the single subjects that represents reward best: A subtraction of “losing-activity” from “winning-activity”. As gamblers are more

depressed than healthy subjects, the degree of depression has been controlled for by taking the depression score as a nuisance variable into the model. Finally the degree of gambling has been included in the analysis.

To show the results of winning per se of all participants we calculate a one-sample T-test of all 24 participants. This is indicated as weighting both reward specific regressors with 1 each, represented as grey bars on top of the design matrix. Results are represented in a T-map, showing the significant voxels of this T-test at a given threshold ($p<0.001$) on a "glass brain".

Results show robust and highly significant activity in reward related areas, the Ventral Striatum and the PFC. The right-sided Nacc peak voxel at (x,y,z: 15, 6, -15mm) shows a maximum activity of $t(18) = 9.75$ while the left one includes two peaks at (x,y,z: -12, 9, -6 mm) with a T-value of $t(18) = 9.03$ and $t(18) = 7.92$ at (x,y,z: -21, 6, -3 mm) (all $p<0.001$, FEW and FDR corrected). The peak voxel of the left PFC is located at (x,y,z: 9, 42 , -6 mm) with a T-value of $t(18) = 4.65$ ($p<0.001$, FDR corrected). These results are striking as almost all significant voxels lie within regions of our a priori hypothesis and indicate a very strong activity by high T-values. The few remaining significant clusters are not part of our hypothesis and are not interpreted.

As the resulting cluster represents reward related activity best, they are used to form a explicit mask that is applied in further calculations. As depression and gambling severity is included into the model, T-values are controlled for both aspects. Fig. 21 shows the specific design matrix and a map of voxels with significant T-values (at the chosen threshold of $p<0.001$) on the upper part and T-maps superimposed on an anatomical T1 slice of a template brain of the MNI on the lower part.



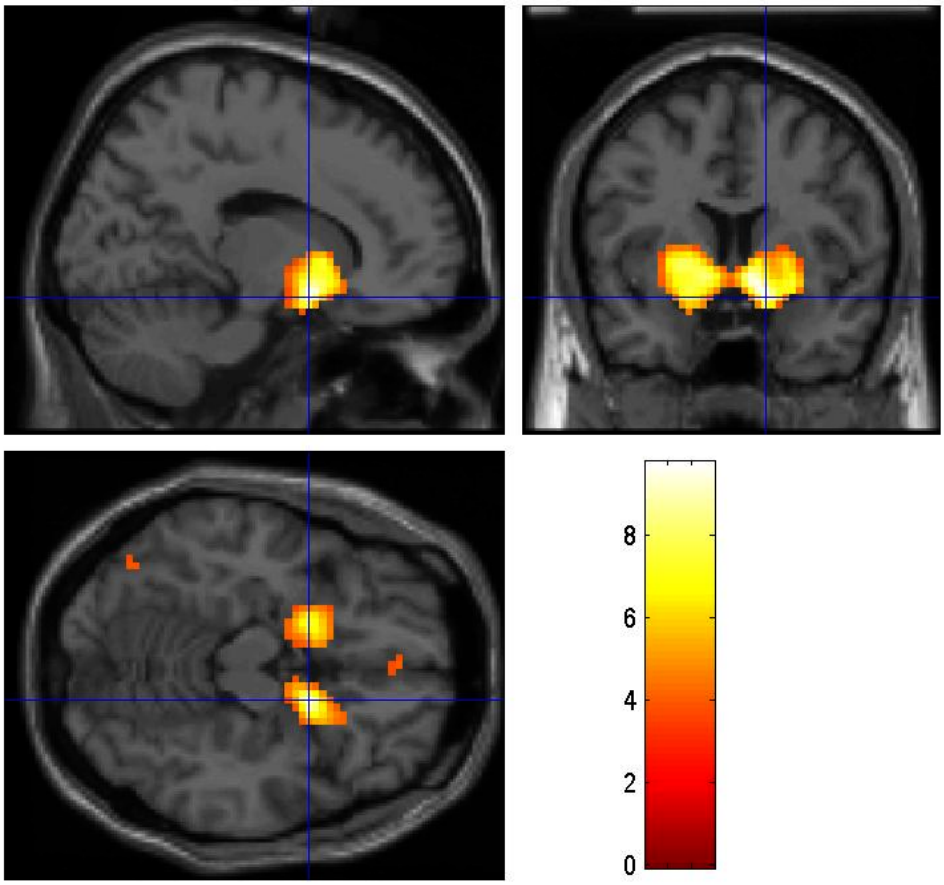


Fig. 21: A T-map representing voxels that shows reward related activity in healthy controls (above: superimposed on a glass brain, bottom: the same results superimposed on a T1 template of a standard brain)

A subanalysis testing for reward activated areas in healthy men:

This one-sample T-test focuses on reward related activity in the control group. Healthy subjects present bilateral prefrontal and Nacc activation. Right-side striate peaks are at (x,y,z: 12, 15, -6 mm) with t(18) = 8.40 and t(18) = 7.82 at (x,y,z: 15, 6, -15 mm), all at p<0.001, both FEW and FDR corrected. The left side peak voxel is located at (x,y,z: -12, 9, -6 mm) with t(18) = 7.56 (p<0.001, FEW and FDR corrected). Left prefrontal peak voxels are at (x,y,z: -9, 42, -9 mm) and (x,y,z: -3, 51, -12 mm), while there the right-side peak voxel is at (x,y,z: 9, 45, 0 mm); (p<0.001, FDR corrected).

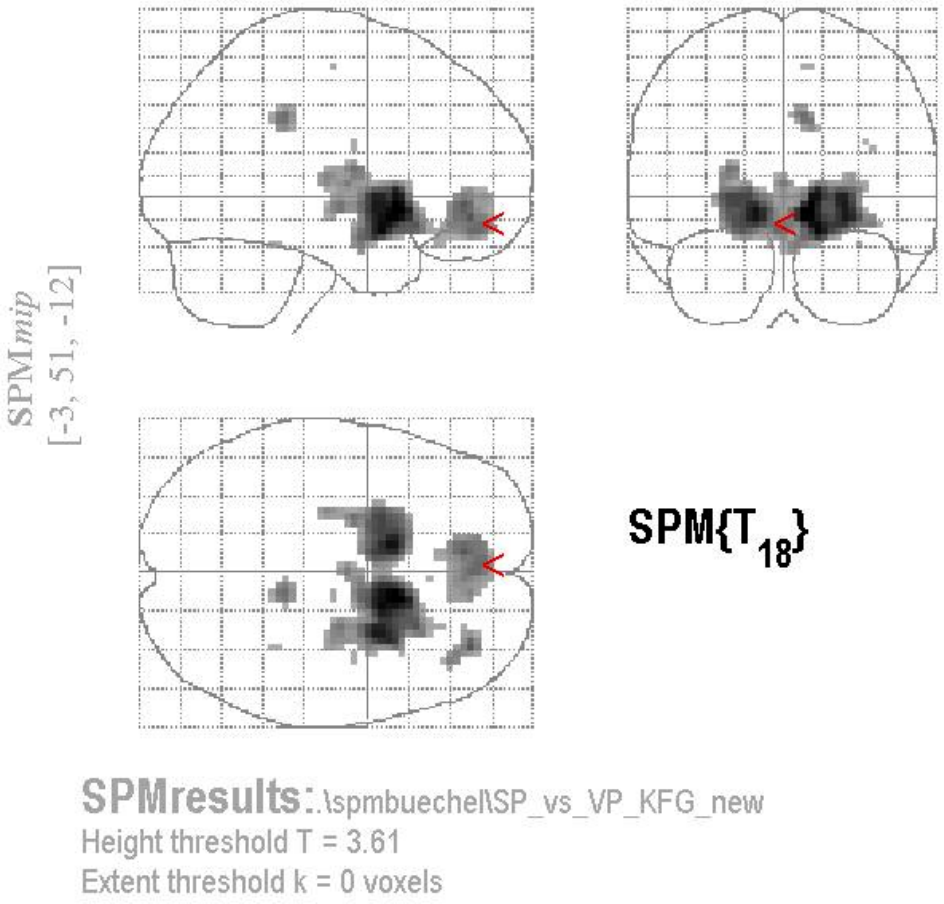


Fig. 22: A one-sample T-test showing reward related activity of 12 pathological gamblers only

Results for gamblers show reduced, but typically located activity. We see striate activity, but no prefrontal activation. Right-side striate peaks are at (x,y,z: 12, 15, -6 mm) with t(18) = 8.40 and t(18) = 7.82 at (x,y,z: 15, 6, -15 mm), all at p<0.001, both FEW and FDR corrected). The left side peak voxel is located at (x,y,z: -12, 9, -6 mm) with t(18) = 7.56 (p<0.001, FEW and FDR corrected).

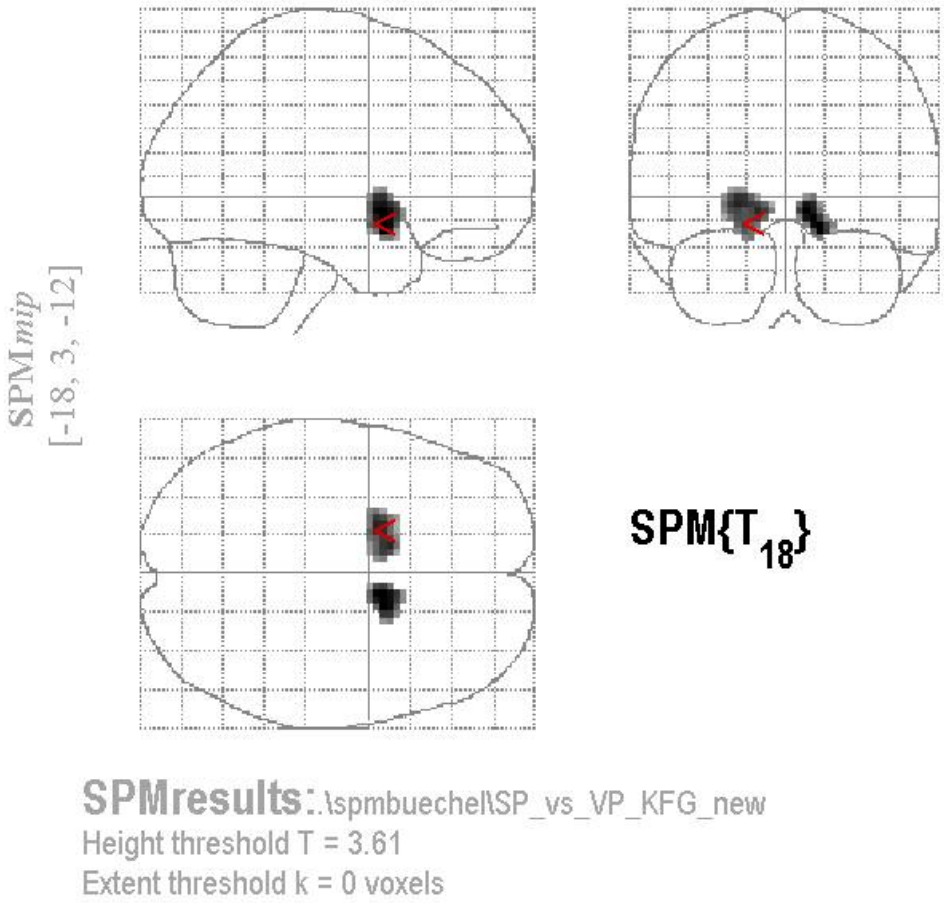


Fig. 23: A T-map representing voxels that reward related activity in pathological gamblers

4.3 Pathological gamblers show striate hypoactivity

According to our a priori hypothesis the data reveals hypoactivity in ventral and prefrontal regions in pathological gamblers. A direct comparison of the Ventral Striatum and PFC of both groups confirms a significant group difference of reward related activity. A two sample T-test is performed by contrasting the regressor representing the gamblers with –1 and the regressor representing the controls with 1. To show the group difference *only for reward related regions* we apply a mask [from the group effect for winning per se at $p<0.001$] to the results of the comparison. All resulting significant voxels represent hypoactivity in reward related activity in pathological gamblers. As we test within an a priori hypothesis related region, i.e. the Ventral Striatum and the PFC we calculate a small volume correction (SVC) with a 10mm radius sphere around left side Ventral Striatum and left PFC peak voxels.

We report two peak voxels from the right Nacc; the centre voxel at (x,y,z = 15, 12, 3 mm) with t(18) = 4.33 and at (x,y,z = 24, 9, 0), (all at p<0.05, FWE and FDR corrected). The left Ventral Striatum group difference is less strong, but still significant. The centre voxel at (x,y,z = -12, 15, -6 mm) only has a value of t(18) = 2.71. Another peak is at (x,y,z = -15, 18, -9 mm) with t(18) = 2.68, both peaks survive FDR correction (p<0.05). The left PFC shows a significant hypoactivity with a peak voxel at (x,y,z = -12, 42, -3 mm) with t(18) = 3.59 and at (x,y,z = -9, 48, -9 mm) with t(18) = 2.84, both FDR corrected.

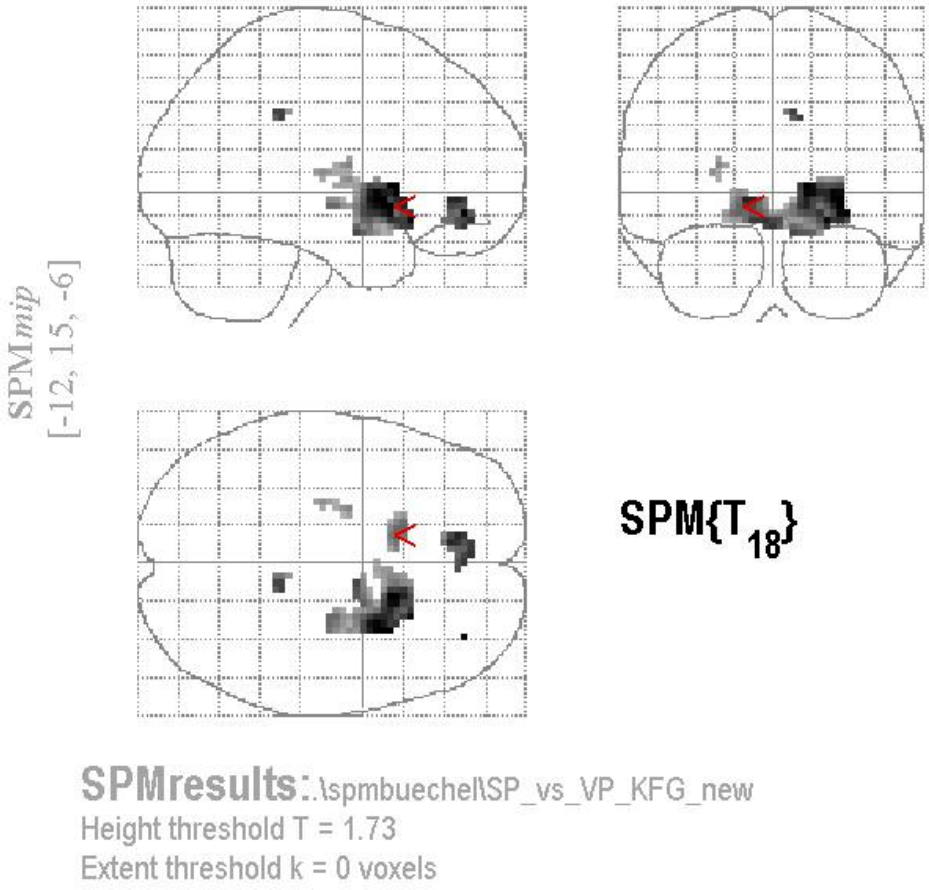


Fig. 24: A T-map representing voxels that show contrasted hypoactivity in reward related activity in pathological gamblers in comparison to healthy controls

4.2. Striate hypoactivity is correlated to gambling severity

Regression analysis of the degree of gambling severity to striate hypoactivity shows significant results.

A regression analysis of striate activity and gambling severity

By contrasting the regressor of gambling severity of pathologic gamblers with –1 in a one sample T-test we calculate a T-map representing voxels that are (according to our hypothesis) negatively correlated to the degree of gambling. A large sample of the bilateral Ventral Striatum hypoactivity is described well by the degree of gambling, thus giving (FDR corrected) significant T-values. Results are masked by the effect of winning per se as in prior calculations. The left Ventral Striatum includes two peak voxels at (x,y,z = -24, 3, -3) t(18) = 4.87 and (x,y,z = -15, 9, 0) t(18) = 4.03, $p<0.05$. The right Ventral Striatum has two peak voxels at (x,y,z = 12, 9, 0) t(18) = 2.89 and (x,y,z = 21, 9, -15) t(18) = 2.36, $p<0.05$. The T-map is shown in Figure below.

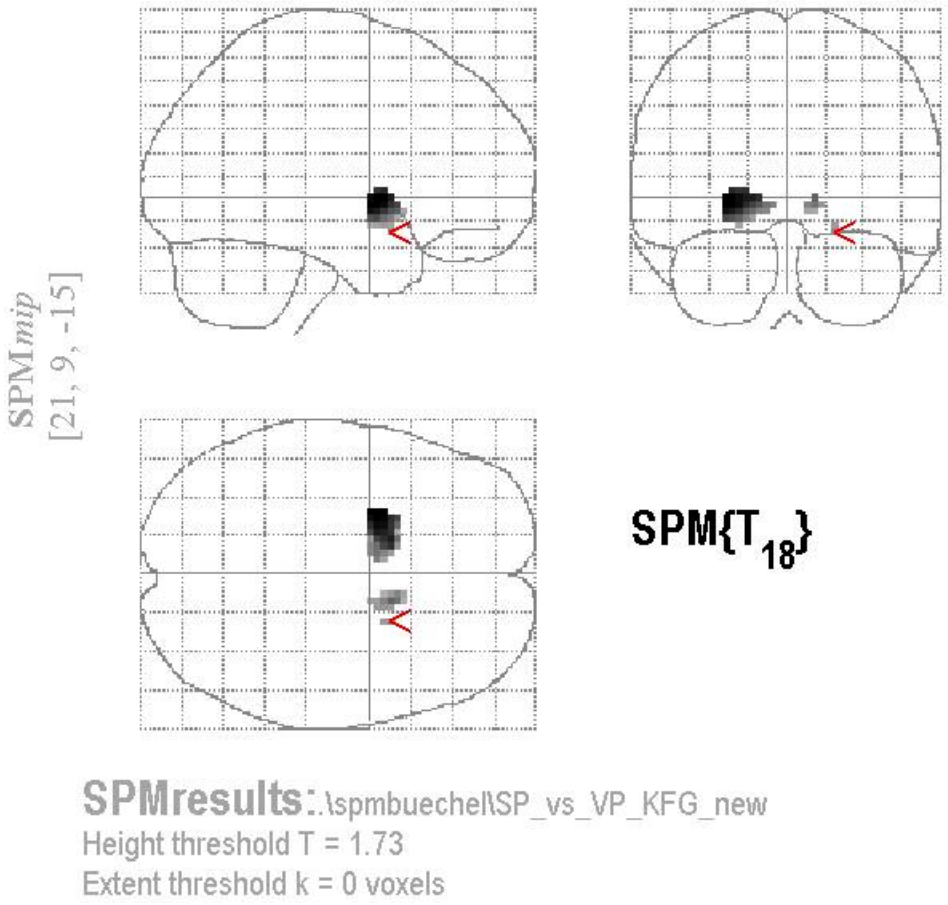


Fig. 25: A T-map representing voxels that are negatively correlated to the degree of gambling in the patient sample masked with the contrast [winning > losing] at P < 0.001

Correlation analysis of peak striate activity and gambling severity

For a true correlation analysis we performed a calculation outside SPM 2. We sampled the individual signal intensities from the peak voxel of the gambling severity

regressions analysis (left Ventral Striatum at (x,y,z = –24, 3, -3 mm) from every gamblers "win-specific"-contrast image. All 12 intensities are correlated and plotted to the gambling severity in a simple excel-calculation with arbitrary units (Fig 26). A highly significant correlation is shown, with a correlation coefficient of r = -0.725 ($p<0.001$). The same calculation could not show significant results for the prefrontal peak voxel.

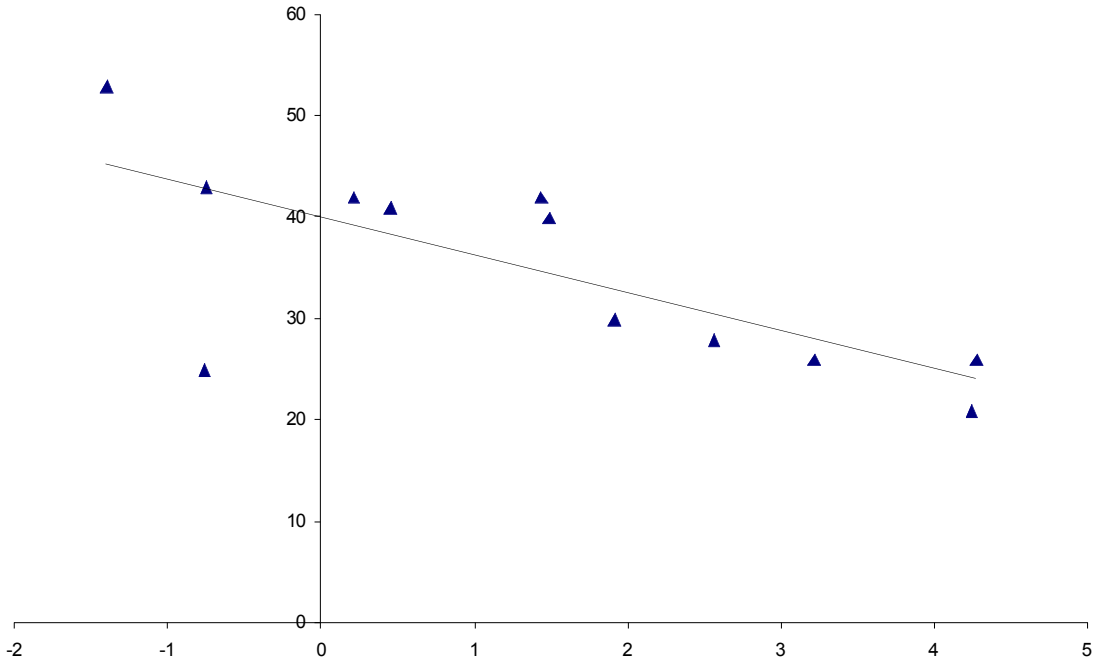


Fig. 26: Correlation analysis of peak striate activity and gambling severity in pathologic gamblers at x,y,z = –24, 3, -3 mm

5. Discussion

5.1 General considerations

While our facts reveal a neural correlate of pathological gambling, they also leave numerous questions to ask. Facts are:

1. Winning money in our gambling task shows an increase of BOLD-signal in reward processing areas i.e. the Ventral Striatum and the PFC.
2. Pathological gamblers show a reduced increase of BOLD-signal in these areas in that task.
3. Severity of gambling correlates to the BOLD-signal in these areas in both healthy controls and pathological gamblers.

It is unclear what exactly our paradigm measures and how efficient it is. We try to interpret in detail what a reduced BOLD-signal of the Ventral Striatum and the PFC means. Furthermore we speculate about the genetic and environmental causes of the underlying neural dysfunction. This implicates further studies which are discussed briefly.

5.2 What exactly activates the Ventral Striatum and PFC during our gambling task?

Our gambling paradigm includes various aspects, i.e. visual and motor aspects, associated emotions, anticipation, strategy and decision making, salience and arousal. It is impossible to measure an isolated cognitive function. However, our chosen contrast represents a comparison of the BOLD signal of the onset of moments when money was gained or lost. This contrast largely eliminates visual, motor, salience and arousal aspects.

Reward processing itself is a complex combination of varying aspects. There are at least two separable phases in reward processing - anticipation (with variations in reward magnitude and probability) and the actual "reward" outcome. Processing the difference of the expected and actual outcome is described in the error prediction model. Varying reward magnitude, probability and outcome allows testing for a wide range of gambling situations and highlight the specific cerebral regions that encode these distinguishable processes. Our paradigm is a fast event related experiment that does not allow a separation of the anticipatory and outcome phase. The need for a fast track of games was necessary to represent a real life gambling situation. Phase that would be long

enough to differentiate the hemodynamic response of the anticipatory and outcome phase would severely slow down the game. We decided to rather have a "powerful gambling"-situation for the price of hemodynamic overlays of psychological distinguishable processes. A human fMRI imaging study by Yacubian et al. used a gambling paradigm that allowed a dissociation of reward and loss anticipation and outcome. It also allowed varying the absolute amount of money as an outcome and its probability to receive it, thus testing the error-prediction for different parameters. Healthy volunteers showed the Nacc to encode for both, anticipation and actual outcome, the latter only if the prediction error is positive. Ventral striatal responses did not express the full range of expected value, but only the gain-related expected value. At reward delivery this area showed a reward probability and magnitude related prediction-error signal. Negative anticipation ("loss-related expected value") and its negative prediction error in regard to the outcome were processed in the amygdala, highlighting the close circuitry of the Nacc and the amygdala (Yacubian, 2006). An encoding of positive anticipation and its prediction error in the reward delivery situation was also seen by Tobler in 2007 (Tobler, 2007).

5.3 What do the areas of interest represent?

We know much about reward processing structures, but single components of the circuitry are hard to define in their isolated function. Also, inferences about dysfunction of certain areas are limited to our incomplete understanding of their normal function. We can surely say that the Ventral Striatum and the PFC are involved in reward processing. Evidence that prefrontal areas are important in decision making and impulse control is also overwhelming. Our results are comparable to findings in alcohol and cocaine addiction disorders (Koob 1992, Tupala 2004, Breiter 1997, Volkow 2000, Dackis 1985).

5.4 What does a decreased BOLD-signal in pathological gamblers mean?

The exact neural correlate of the BOLD signal stays speculative. Multi-modal studies clearly showed that changing neural activity does cause a change of blood flow. Logothetis et al. found that the BOLD-signal represents neural input and intracortical processing rather than "spiking" output (Logothetis, 2001). This rises the question if the hypoactive neurones lie inside our regions of interest or only project to them (e.g. from

the midbrain/VTA). This would be concordant neuroanatomically with dopaminergic projections from the brainstem to the Ventral Striatum and the PFC.

While a PET study shows specific receptor and metabolism profiles, the BOLD-signal gives no further information about its related neural activity. We do not know the affected structure or transmitter system. However, we do know that the hypoactive regions are innervated by dopaminergic neurones. We cannot make inferences about more detailed dysfunctions, such as which dopaminergic or dopamine-related substructure is deficient. Receptor structure and receptor density are believed to be altered in hypoactive dopaminergic reward related areas, these structures again relate to different genes or their enzymes of transmitter-production, transmitter-recycling or up-taking and further substructures. As we only use individual contrasts for the group analysis, we have no figures about absolute activity in the regions of interest. We can only state that the activation difference from winning compared to losing is lower in pathologic gamblers, which does not mean pathologic gamblers have a general lower activity state in the regions of interest. This lack of absolute quantification makes it harder to interpret a hypoactive reward system.

5.5 What causes a dysfunction of the reward system?

Regarding PET and genetic studies it is likely that genetically and/or extrinsically altered dopaminergic receptors in reward related areas can enforce risk-taking behaviour including pathological gambling. Genetic studies have shown certain polymorphisms to cause altered receptor adherence and density. Behavioural studies show pathological gamblers often come from low social background and face problems like immigration and unemployment. While genetic decoding is fairly simple, environmental impact on reward processing is harder to quantify. Animal studies show the amount of neurons and connectivity to differ in relation to a rich vs. poor environment (Walsh, 1981). Human neuroimaging studies indicate grey matter volume changes as a detectable neural correlate of various environmental influences (Maguire, 2003). In regard to the chicken and egg problem, we cannot state pathologic gambling alters the Ventral Striatum or vice versa. We showed that addictive non-substance behaviour can cause neural changes that compare to the ones of drugs of abuse. Pathologic gambling, like most other psychiatric pathologies appear to be caused by multifactorial intrinsic and extrinsic factors.

5.6 Which diagnostic consequences can be derived from this study?

It is not clear if pathological gamblers form one group at all or could at be sub-typed. This study did not use questionnaires to investigate sub-typing. The results do not suggest various groups of gamblers. We recommend the use of questionnaires that test for personality traits such as risk taking behaviour and novelty seeking for a better understanding of their personality traits. If pathological gambling is an addiction or an impulse control disorder has far consequences. Insurance companies will pay differently depending on how national health system define and classify pathological gambling. This study gives evidence on both aspects (addiction and impulse control disorders) and raises the question if they can or should be separated at all. Striate dysfunction points to classical substance related addictive behaviour while prefrontal dysfunction points to a reduced impulse control and related impulse control disorders. Comorbidities can be found on both sides of the spectrum, like alcohol and cocaine addiction and obsessive-compulsive behaviour.

5.7 Which therapeutic consequences can be derived from this study?

The most common treatment is customised behavioural psychotherapy that includes treating comorbidities. Supporting psychopharmaceutical therapy is established, yet remains experimental. Finding the Ventral Striatum as a neural correlate, further research of dopaminergic, serotonin and glutamate transmission in this region could give further therapeutic options. Finding a neural correlate of a pathological state is also a chance to monitor therapeutic results. One could test if various therapies show changes in these regions.

5.8 Which further studies should be made?

Diffusion tensor imaging (DTI) could show functionality of white matter/connecting tissue of reward related regions, nuclear magnetic resonance imaging (NMR) could show transmitter concentrations within the reward related brain areas. PET/SPECT studies might detect receptor specific changes in the dopaminergic and other transmitter systems in more detail. More and other polymorphisms in dopaminergic transmission should be identified and put in relation to personality traits and gambling behaviour. For investigation of actual structural changes, samples of dopaminergic tissue could be analysed if a pathological gambler agrees on this as part of a biopsy. The gender

difference in gambling behaviour and prevalence is highly important. The influences of sex hormones on reward related transmitters should get more attention. Yacubian at al. excluded female volunteers in a gambling paradigm due to Pasqualini´s findings that women have an increased endogenous striatal dopamine concentration (Pasqualini et al., 1996). Our study only included men as well; however we suggest including female pathological gamblers in future studies and highlight gender differences in ventral striate dopamine processing. Further studies on pathological gambling should include interviews for gambling sub-typing, a more detailed severity quantification, personality typing, comorbidities and diagnostics along somatic markers like drug screening and arousal signs (pulse, skin conductance).

5.9 Which further recommendations can we make?

The distinct results support the idea that pathologic gambling resembles to substance based addictions and is pathophysiologically closer to these psychiatric diseases (ICD-10: F10 – F19). This implicates therapeutic approaches that compare to those we know from alcohol and other substances of abuse, including primary and secondary prevention, monitoring, treatment and research on pathologic gambling on all levels. School-prevention must include special features of adolescent gambling such as excessive computer game and internet use. One should offer students healthy alternatives to gambling, such as making music, art, sports, field trips and other after-school activities. All groups of people that are confronted with pathological gamblers must be aware of the severity of symptoms and be professional about specific treatment options of pathological gambling. That is especially true for general physicians, casino staff, financial and credit institutes, psychologists and many others. As there is a recreational and accepted side of gambling, drawing the line between use and abuse must be clarified. Health-care-politics should decrease options of gambling and improve information supply and safety features in gambling places. This could be done by standardised warning and information material similar to tobacco handling. With a high tax income from gambling, a higher percentage of the money could be well invested in research of causes, diagnosis, types and treatment of pathological gambling.

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Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach der Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe.

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Berlin, 07. Juli 2011

Jan Reuter