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Functional neuroanatomy of the
evaluation of motivational significance:
An orbitofrontal perspective.

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I. Summary (German)

Obwohl der orbitofrontale Kortex bisher stets als entscheidende kortikale Instanz bei der Verarbeitung von Belohnungen angesehen wurde (vgl. Rolls, 1999), lässt sich aufgrund verschiedener Befunde annehmen, dass zumindest posterioren Anteilen dieses Areals eine allgemeinere Rolle bei der Integration salienter motivational relevanter Informationen in adaptives Verhalten zukommen könnte (z.B. Elliott et al., 2003). So führten beispielsweise seltene <u>unbelohnte</u> Ereignisse, die eine umgehende und schnelle Verhaltensanpassung erforderten, zu Aktivierungen in posterioren Anteilen des orbitofrontalen Kortex unabhängig von deren hedonischer Valenz (Gruber et al., 2006, in prep.). Um diese Annahme bezüglich einer allgemeineren Funktionalität des posterioren orbitofrontalen Kortex zu überprüfen, wurden in der von mir durchgeführten Studie die Präsentation verschiedener Arten verhaltens- bzw. motivational relevanter Stimuli mit unterschiedlicher hedonischer Wertigkeit systematisch innerhalb eines Aufgabenwechselparadigmas variiert. Auf diesem Wege sollten in einem direkten Vergleich zwischen motivational relevanten Stimuli mit einer Belohnungsassoziation und seltenen neutralen Stimuli, die eine umgehende Verhaltensanpassung erforderten, innerhalb derselben Studie insbesondere Gemeinsamkeiten – und gegebenenfalls auch Unterschiede – in der neuronalen Repräsentation belohnungsassoziierter Stimuli und verhaltensrelevanter seltener Stimuli aufgedeckt werden.

Zehn gesunde Probanden (5 Männer und 5 Frauen) nahmen an der vorliegenden Studie in einem 3-Tesla Magnetresonanztomographen teil. Die Probanden führten ein sogenanntes Aufgabenwechselparadigma durch, bei dem sie verschiedene farbige Schlauchfiguren (bivalente Stimuli) entweder im Hinblick auf deren Form (2 mögliche Formen) oder deren Farbe (4 verschiedene Farben) beurteilten. Die zwei Figuren (Formaufgabe) und zwei der präsentierten Farben (Farbaufgabe) waren dabei jeweils immer mit einer linken bzw. rechten Antworttaste verbunden und wurden häufig in beiden Aufgaben präsentiert. Die übrigen zwei Farben wurden dagegen absolut <u>selten</u> präsentiert und erschienen <u>ausschließlich in der Formaufgabe</u>. Diese „kritischen seltenen Ereignisse" waren entweder:

(1) irrelevant (d.h. Probanden waren instruiert, diese Ereignisse zu ignorieren und entsprechend der Formaufgabe zu antworten)

(2) irrelevant und **mit einer Belohnung assoziiert**

(3) **verhaltensrelevant** (d.h. Probanden waren instruiert in diesem Falle eine entsprechende Verhaltensanpassung vorzunehmen und eine andere Taste zu drücken als ursprünglich durch die Formaufgabe gefordert) oder

(4) **verhaltensrelevant** und **mit einer Belohnung assoziiert.**

Die Hälfte der verbleibenden experimentellen Durchgänge war ebenfalls mit einer Belohnung assoziiert und somit motivational relevant. Die Belohnungsassoziation an sich war deshalb nicht selten. Um die Probanden davon abzuhalten einzelne Belohnungen mitzuzählen, wurden die Probanden nicht direkt belohnt, sondern wurden aufgrund ihrer durchschnittlichen Performanz (d.h. die gemittelten Reaktionszeiten und Fehlerraten) in „Belohnungsdurchgängen" innerhalb einer Rangliste aller Teilnehmer platziert. Die drei Bestplatzierten konnten dabei eine Belohnung von € 50 gewinnen, was einen entsprechenden Anreiz für die Optimierung der Performanz in belohnungsassoziierten Durchgängen darstellte.

Die Verhaltensdaten wurden mit SPSS (Version 13.0) ausgewertet. Die funktionellen Bilder wurden mit Hilfe von SPM2 vorverarbeitet und analysiert.

Auf der Verhaltensebene führte die Präsentation seltener verhaltensrelevanter Ereignisse zu einer signifikanten Zunahme der Reaktionszeiten und Fehlerraten. Im Gegensatz dazu hatte die Belohnungsassoziation keinen signifikanten Effekt auf die Performanz der Probanden. Darüber hinaus zeigte sich, dass der rechte posteriore orbitofrontale Kortex (im Bereich des posterioren olfaktorischen Sulcus sowie direkt angrenzender posteriorer Bereiche) in ähnlicher Weise durch verschiedene Arten verhaltensrelevanter Ereignisse aktiviert wurde (d.h. sowohl durch Ereignisse mit einer Belohnungsassoziation also auch durch verhaltensrelevante seltene Ereignisse). Gleichzeitig fand sich jedoch auch eine gewisse Selektivität innerhalb des orbitofrontalen Kortex. Aktivierungen innerhalb weiter lateral gelegener Areale des posterioren orbitofrontalen Kortex und angrenzender Bereiche des frontalen Operkulums sowie auch Aktivität im rechten anterioren orbitofrontalen Kortex konnten entsprechend nur dann beobachtet werden, wenn ein seltenes Ereignis auch verhaltensrelevant war und eine umgehende Verhaltensanpassung erforderte. Im Gegensatz dazu fand sich Aktivität im linken medialen orbitalen Gyrus ausschließlich in Assoziation mit einer Belohnung.

Nach den Ergebnissen einer kürzlich durchgeführten Metaanalyse (vgl. Kringelbach & Rolls, 2004) werden verschiedene Aspekte der Verarbeitung motivational relevanter Ereignisse tatsächlich von unterschiedlichen orbitofrontalen Subarealen

repräsentiert. Im Hinblick auf die vorliegenden Ergebnisse lässt sich deshalb annehmen, dass die selektiven Aktivierungen in lateral posterioren orbitofrontalen Arealen (und frontooperkularen Kortizes) sowie im linken anterioren orbitofrontalen Kortex mit der aktiven Verhaltensanpassung an verhaltensrelevante seltene Ereignisse assoziiert waren und somit die Flexibilität im Verhalten garantierten, während der linke mediale orbitofrontale Kortex wahrscheinlich selektiv in die Repräsentation der positiven hedonischen Wertigkeit der Belohnung involviert war (siehe auch: Kringelbach, 2005). Darüber hinaus erscheint es zudem gerechtfertigt, für die Aktivierungen im rechten posterioren orbitofrontalen Kortex (innerhalb des posterioren olfaktorischen Sulcus sowie in direkt angrenzenden Gebieten), die sich sowohl in Verbindung mit seltenen verhaltensrelevanten Ereignissen als auch im Zusammenhang mit einer Belohnungsassoziation zeigten, tatsächlich eine allgemeinere Rolle bei der Repräsentation salienter verhaltens- bzw. motivational relevanter Ereignisse anzunehmen (vgl. Kringelbach und Rolls, 2004).

Abschließend lässt sich somit sagen, dass die vorliegenden Ergebnisse die initial formulierte Hypothese bezüglich einer allgemeineren Funktion des posterioren orbitofrontalen Kortex bei der Repräsentation salienter verhaltens- bzw. motivational relevanter Ereignisse unabhängig von deren hedonischer Wertigkeit weitgehend bestätigen konnten. Dennoch fanden sich auch selektive orbitofrontale Aktivierungen, welche vermutlich auf Unterschiede in der hedonischen Wertigkeit der in der vorliegenden Studie präsentierten motivational relevanten Ereignisse sowie auf deren jeweilige Konsequenzen im Hinblick auf das Verhalten (aktive Verhaltensumkehr nur bei verhaltensrelevanten seltenen Ereignissen) zurückzuführen sein dürften.

II. Summary (English)

Low-frequency events that required a rapid behavioral adjustment regardless of a reward association have been shown to activate the posterior orbitofrontal cortex (Gruber et al., 2006, in prep). In addition, this region was also activated by both salient rewards and penalties independent of their actual hedonic valence (Elliott et al., 2003). This led to the assumption, that the observed orbitofrontal activation could in fact underlie a specialized mechanism for the processing of significant events in the environment, which does not emerge exclusively in the context of (positive) reward, but whenever any kind of salient motivationally (or behaviorally) relevant event occurs that may require a rapid behavioral adjustment. In order to test for this assumption in the present study the exact nature of motivationally (or behaviorally) relevant events presented in the course of a task switching paradigm was systematically varied. This allowed me to directly compare neural mechanisms involved in the processing of biologically significant events that signaled the chance to gain a reward for correct performance, with neural responses to behaviorally relevant low-frequency events (oddballs) that required an adaptation of motor-behavior (button-press), however without being rewarded.

Ten healthy subjects (5 females & 5 males) underwent functional magnetic resonance imaging on a 3-Tesla-MRI-Scanner. Participants had to perform a cue task-switching experiment in which they had to respond to either the color or the shape of abstract geometric objects. Thereby, one out of two different objects was presented in one out of four different colors during the experiment (bivalent stimuli). The two objects and two of the colors (blue and red) were always mapped to a left or right manual response and appeared frequently in both tasks. The remaining two colors (white and yellow) were exclusively presented in the shape task and represented the "critical low-frequency events" (oddballs), that were either:

(1) irrelevant (i.e., had to be ignored and subjects had to respond to the respective shape)

(2) irrelevant and **associated with reward**

(3) **behaviorally relevant** (i.e., subjects had to adjust their behavior accordingly by pressing a different response button than initially required by the shape task)

(4) **behaviorally relevant** and **associated with reward**.

Half of the remaining trials were also associated with a reward and were therefore behaviorally relevant. However, reward was no low-frequency event in itself. Further, in order to prevent subjects from counting individual rewards, trials were not immediately rewarded, but instead reward was determined by a ranking-list of all participants, which was based on the overall mean performance in rewarded trials. Only the best three subjects with regard to their mean reaction times and error rates in rewarded trials got an additional payment of € 50 each, which created the incentive for optimization of performance in reward trials.

The behavioral data were analyzed with SPSS (Version 13.0). Preprocessing of the neuroimaging-data was done using SPM2.

The behavioral data revealed that behaviorally relevant oddballs led to a significant increase in both reaction times and error rates. In contrast, the reward association did not significantly affect behavioral performance. On the neural level, the subtraction contrasts including different types of behaviorally relevant events (i.e., both behaviorally relevant oddball events and events with a reward association minus congruent shape trails) revealed a significant activation in the right posterior orbitofrontal cortex (directly adjacent to and within the right posterior olfactory gyrus). In addition, two more laterally located posterior orbitofrontal clusters which further extended into the frontal opercular cortices and one cluster in the right lateral anterior orbitofrontal cortex were exclusively activated by relevant oddball events which required a behavioral adjustment, while the reward association specifically activated the left medial orbital gyrus.

Considering the results of the meta-analysis by Kringelbach & Rolls (2004), distinctive orbitofrontal subregions may represent different aspects of processing of motivationally relevant stimuli. Accordingly in the present study, selective activations in lateral posterior orbitofrontal cortices (extending into frontoopercular cortices) and left anterior orbitofrontal cortex presumably guaranteed behavioral flexibility that ensured the adequate behavioral adjustment towards the response-relevant oddball event, while the activation in left medial orbitofrontal cortex, that occurred exclusively in the context of reward, may be interpreted in terms of a representation of the positive hedonic value of the correct answer to a stimulus that was associated with a rewarding outcome (cf., Kringelbach, 2005). Finally, with regard to the right posterior orbitofrontal cortex (within and adjacent to the posterior olfactory sulcus), which was activated by different types of behaviorally relevant

events in a similar way, it may now be warranted to infer that its function may be best described as that of a candidate region for the representation of salient behaviorally relevant events in general (see also: Kringelbach & Rolls, 2004).

In conclusion, the results provide first support for the initial proposal of a neural mechanism located in the right posterior orbitofrontal cortex that may indeed be assumed to be specialized for the processing of biologically significant events in general, regardless of their actual (hedonic) valence. Nevertheless, reward and behavioral relevance of infrequency also activated distinctive orbitofrontal subareas, a finding which may be explained by differences in hedonic valence and behavioral consequences of the different types of behaviorally relevant events presented in the current study.

III. Introduction

Adaptive behavior requires adequate reactions to the demands of an ever-changing environment. Accordingly, organisms pursuing goal-directed behavior have to face two antagonistic challenges that need to be balanced in a context-sensitive way: The first one is to maintain goals in the face of distracting stimuli and competing responses, while the second one is the ability to flexibly switch between goals and reconfigure behavioral dispositions whenever a relevant change is detected (cf., Goschke, 2003). The ability to react rapidly and adequately to significant events in the environment often decides upon behavioral success and guarantees survival. Consequently, all salient changes (e.g., unexpected, aversive or novel events), which could be of greatest potential relevance to current or planned behavior (Downar et al., 2001), bear a strong potential to capture the organism's attention involuntarily and trigger an immediate reallocation of attentional and/or behavioral resources (cf., Redgrave et al., 1999a). For instance, a browsing animal in the savannas of Africa would involuntarily attend to the sudden sound of an approaching predator and would then probably decide for an instant flight as otherwise it would end up as prey, while an unexpected encounter with a potential mate would similarly capture attention involuntarily, but instead lead to active mating behavior. Finally, the sound of a bus carrying tourists on a photo-safari would also immediately draw the animal's attention, but would almost certainly not lead to any behavioral change at all. These examples show, that it is vital to respond to changing environmental demands in a context-sensitive fashion, as not every salient event requires an identical behavioral adjustment or even necessitates an adjustment at all. Hence, an organism also has to be able to evaluate the behavioral relevance of a salient change against the background of its actual meaning for the organism's needs, since only adaptive behavioral decisions will guarantee survival and successful reproduction.

In a real world environment animals mainly appraise the actual behavioral relevance of environmental changes by their expected positive or negative value and use this information for the subsequent behavioral modification. Especially the orbitofrontal cortex [Abbr. OFC] has been assumed to be the prime cortical region that influences goal-directed behavior, cognitive control processes and behavioral decisions based on information concerning the perceived reward value of environmental stimuli (cf., Kringelbach & Rolls, 2004; Rolls, 2004).

In an experimental setting arbitrary stimuli can also acquire behavioral relevance (e.g., through association with a button press). For instance, in laboratory-animals the assignment of behavioral relevance to experimental stimuli is commonly achieved through instrumental or classical conditioning by making use of primary rewards (i.e., congenital forms of rewards that are of direct importance for survival and/ or reproduction, like for example food stimuli), in that way that a response made to a certain stimulus is associated with a primary reward and therefore acquires a reward value. Conversely, in humans it is also possible to make a stimulus relevant in the experimental context by the means of a simple verbal instruction without providing any incentive associated with this particular stimulus. Interestingly, these unrewarded "cognitive incentives" have under some circumstances also been found to be associated with an orbitofrontal response, namely when they were both perceived as considerably salient (like for example infrequent or novel events) and were also relevant for the organism's behavior (e.g., Gruber et al., 2006, in prep.; Schnider et al., 2005). Based on these prior findings, which underlined the orbitofrontal responsiveness to different forms of salient behaviorally relevant stimuli, the current thesis was intended to examine whether the OFC plays a more general role in the representation of behavioral relevance of salient stimuli and whether it is therefore also responsive to salient stimuli outside of the context of reward processing in case these stimuli are also perceived as relevant by the organism.

The central interest of this thesis therefore lay on the orbitofrontal cortex and its role in processing of different forms of salient behaviorally relevant stimuli (like rewarded stimuli or infrequent deviants). However, before the main topic will be addressed, the reader of this thesis will be provided with a basic understanding of the terms 'salience' and 'behavioral relevance', because these two concepts will be addressed throughout the whole manuscript. Subsequently, the second section of the introduction will provide the reader with an outline on the neural correlates of reward processing and their respective functions within the context of motivational behavior, before the basic functions of the OFC within the motivational network will be described in further detail in the third section. Section 3 of the introduction will include information on the OFC's neuroanatomical connectivity and will further focus on orbitofrontal processing of reward value in a context-sensitive way providing the actual basis for flexibility in cognitive-control processes in motivational behavior. In addition, a short excurse to findings on orbitofrontal

processing of other forms of salient behaviorally relevant events outside of the context of reward processing is provided. After that, a comprehensive outline will be given that deals with other brain regions, which have been found to be involved in the detection and supposedly also the evaluation of other forms of salient and behavioral relevant events, mainly in the context of oddball studies. Further, it will be also outlined, why orbitofrontal activations have not been commonly observed in the oddball paradigm. Finally, section 4 of the introduction will delineate the two main working hypotheses against the background of previous findings and will also illustrate the rationale of the current thesis.

1. Conceptual definition of "salience" and "behavioral relevance"

A fundamental neural organizing principle of human information processing is the preferential processing of significant information in the environment. The term "significance" is generally referred to as a stimulus property that allows the stimulus or event to rise as a signal above the noise of incoming information. Neural mechanisms involved in significance processing have been assumed to actively weigh stimuli according to the core motivations of the organism and thereby resolve competition among the various sources of potential input from the external and internal environment. More importantly, it has been assumed that significance processing has been shaped by natural selection and underlies the most fundamental motivation that is to minimize danger or threat and to maximize pleasure or reward (cf., Williams, 2006). However, significance processing involves several steps along a temporal continuum with early preattentive processing of sensory input (e.g., **salience** processing) and later procedures that involve conscious goal-directed processing of salient input (e.g., assignment of motivational and **behavioral relevance**; cf., Williams, 2006). This means that "significance" may be best described as a compound of both salience and behavioral relevance.

Detecting changes in the environment requires a rapid allocation of attention to either objects, features or locations, and an equally rapid disengagement of attentional processes (Bledowski et al., 2004). Unexpected, infrequent or novel events, regardless of their actual task relevance, have been found to elicit a reflexive neural response in healthy participants, which may be similar to the classic

conceptualization of an orienting reflex (Kiehl et al., 2005a; see also: Williams, 2006). By orienting to change one is able to learn about new or unexpected stimuli and events in the environment. Once the input is familiar, it no longer generates the orienting reflex (cf., Williams, 2006). The orienting reflex has been reported to be elicited automatically and leads to an attentional switch (e.g., Näätanen, 1990), which can for instance be measured by an increase in the level of autonomic arousal (e.g., skin-conductance increases and heart rate modulations; e.g., Williams et al., 2000; see also: Boucsein, 1992). It is further assumed to be triggered by the detection of a **salient** environmental stimulus, which strongly deviates from the neuronal model built from the repetitive features of the environment (cf., Sokolov, 1963) and is believed to occur pre-attentively. For instance, midbrain dopamine neurons have been observed to already respond to a salient visual event even before there is an opportunity to make a visual saccade, i.e., before the stimulus is actually foveated. These neurons are simply activated by the unexpected and therefore salient change in the environment, but the precise nature (whether the environmental change is relevant or actually irrelevant to the organism) remains at that time still undetermined (cf., Horvitz, 2002).

Accordingly, the meaning of the term **"salience",** as it will be used in the present study, therefore may be best described as the striking quality of an object that captures an organism's attention automatically, and involuntarily leads to a switch in attentional resources (cf., Redgrave et al., 1999a). It can thereby either be stimulus-inherent or context-dependent. Zink et al. (2004) defined it

> **"[…] as arousing by virtue of either its inherent properties when they are striking or its importance based on the context in which it is presented." (Zink et al., 2004: p. 512),**

while Downar et al. (2002) gave a more elaborate definition in that

> **"The salience of a given stimulus reflects its potential relevance to behavior and is therefore influenced by behavioral context. […] salience may also depend on factors independent of behavioral context, such as stimulus intensity, frequency of appearance, or novelty." (Downar et al., 2002: p. 615),**

which can be further described within the more general framework of

> **"attention [which] is, in part, a mechanism for selecting the features of the sensory environment which are most salient – i.e., of greatest potential relevance to current or planned behavior." (Downar et al., 2001: p. 1256).**

This means that the salience of a stimulus may also be modulated by higher order cognitive processes prior to the eliciting event (cf., Horvitz, 2002). In a situation, in which subjects are instructed to detect infrequent target stimuli (e.g., in the classical oddball paradigm; see Section 4, below) different attentional processes are assumed to interact with each other. On the one hand, infrequent targets are salient due to their rareness and automatically elicit an orienting reflex which has been described as a "bottom-up" or stimulus-driven mechanism, while on the other hand these targets also represent prospective memory goals and for that reason represent a behavioral goal which requires a voluntary adjustment of attentional and behavioral resources in the sense of "top-down" processing (cf., Corbetta & Shulman, 2002). As a result, the detection of salient stimuli that require a behavioral response has been reported to be associated with orienting processes that are often stronger and more robust than the response to novel stimuli (cf., Sokolov, 1963). The term "**behavioral relevance**", in the sense in which it is used in the current study, is therefore a stimulus-characteristic that can exert a rather "top-down" modulatory influence on stimulus salience (Downar et al., 2001, 2002). Stimuli are behaviorally relevant if they constitute a <u>behavioral goal</u> for the organism (e.g., through their association with a punishing or rewarding outcome) and require a <u>behavioral adjustment</u> (e.g., a behavioral change to initiate avoidance or approach behavior). If for instance – like in a previous study (Gruber et al., 2006, in prep.) – an infrequent stimulus acquired behavioral relevance through the simple verbal instruction to execute a special motor response on its appearance, then this stimulus acquires motivational and behavioral significance (i.e., it becomes a prospective memory target) and stimulus salience is probably also increased which adds to its already salient stimulus-characteristic of being rare.

Rewards (e.g., money) always bear the inherent property of being relevant to the organism and its behavior, because they are directly associated with the fundamental motivation of maximizing reward and minimizing punishment, which guarantees survival (cf., Williams, 2006). In most situations in a real world environment, organisms are further required to interrupt ongoing behavior and (rapidly) adjust attentional resources and behavior in order to gain and consume the respective reward (cf., Redgrave et al., 1999a). Rewards therefore represent an <u>ecologically valid situation</u> of **behavioral relevance** different from the strictly experimental form described above (Gruber et al., 2006, in prep.). Still, their salience may vary according to the respective context in which they occur (e.g., whether a monetary

reward occurs unexpectedly or can be predicted) and so does their actual motivational and behavioral relevance. Accordingly, a satiated organism would assign lower motivational and behavioral relevance to a food item than one that is near starvation.

2. Parsing the neural components of reward processing and motivated behavior

On the neural level the identification of reward-predicting stimuli or rewarded events is ensured by the brain's reward circuit, which also guarantees the adequate selection and initiation of goal-directed behavior to acquire a reward (cf., Kalivas & Nakamura, 1999). Initially, incoming sensory information is thereby analyzed for its potentially rewarding or aversive qualities and its reward-predicting attributes (partly based on previous experiences), which allows the identification of positive reinforcers. In a second step, an adequate behavioral response has to be selected against the background of both situation-specific demands and previous experiences within similar situations. If more than one behavioral possibility exists, the expected reward tied to each of the possible responses in the current context is validated and is assigned a motivational value (cf., Redgrave et al., 1999b), which finally allows for the context-adequate and goal-directed selection of a behavioral response (cf., Robbins & Everitt, 1996; Kalivas & Nakamura, 1999; Rolls, 1999).

Motivated behavior therefore relies on several complex and partly interacting processing steps that have to be integrated by the organism's brain. Research findings have provided evidence that not a single cortical region, but a "motivational network" of interacting subcortical and cortical brain regions underlies reward processing and motivated behavior. Among them are for one thing the **midbrain dopamine system** (i.e., substantia nigra and ventral tegmental area [Abbr. VTA]), the **amygdala**, the **OFC**, the **insular cortex**, the **ventral and dorsal striatum** (in particular caudate nucleus and nucleus accumbens) and the **hypothalamus** which are assumed to function in concert (cf., Kringelbach & Rolls, 2004; McClure et al., 2004a; O'Doherty, 2004), even though the exact interactions are still under discussion. Yet, each region also participates with unique functions in the overall implementation of motivational behavior and not all of these regions are assumed to be involved in the actual reward identification and evaluation, but rather provide

important input and output systems for reward-sensitive regions (cf., Kringelbach & Rolls, 2004).

2.1 The regions of the brain's reward circuit

Important input required for motivational processes is for instance provided by the **insular cortex**. Within the "motivational network" the insula mainly supplies higher order processing regions like the OFC with information based on the sensory properties of rewarding stimuli (e.g., odor identity; O'Doherty et al., 2000) and has further been observed to be activated by sensory-specific satiety effects in some studies (O'Doherty et al., 2000; Small et al., 2001; Kringelbach et al., 2003). In contrast, the **hypothalamus** probably functions as a central output structure, which has been assumed to regulate and modulate autonomic and physiological responses to emotional stimuli receiving its input from other structures of the "motivational network" (e.g., the VTA and the nucleus accumbens; Menon & Levitin, 2005).

Midbrain dopamine projections are another input source that is linked to the striatum and cortical regions. Traditionally, these neurons have been reported to be the major source for the release of a teaching signal that indicates an error in reward prediction. In this scheme, the appearance of an unexpected reward elicits a strong dopamine response, while expected rewards do not. Further, unexpected reward omission leads to a suppression of activity in dopamine neurons, presumably providing the organism with important information concerning the future detection and prediction of positive reinforcers in the environment (cf., Schultz, 2000). In humans support for this assumption has mainly been derived from neuroimaging studies addressing dopamine target sites in the striatum (e.g., nucleus accumbens) and also in the orbitofrontal cortex (Berns et al., 2001; Tobler et al., 2006; Abler et al., 2006). Of these structures, the **ventral striatum** (and in particular the **nucleus accumbens**) has been reported to convey the motivational significance of emotionally laden stimuli (e.g., Knutson et al., 2001a) also in form of a reward-prediction error (Abler et al., 2006) and has been assumed to participate in both Pavlovian and instrumental conditioning (O'Doherty et al., 2004), while the **dorsal striatum** including **anterior caudate nucleus** has been further observed to mediate the instrumental component of motivated behavior (Elliott et al., 2004; O'Doherty et

al., 2004). Striatal function may thereby be best described in terms of the "actor-critic-model" in which the ventral striatum has the function of the "critic", that learns to predict future rewards based on the reward-prediction error, while the "actor" (i.e., the dorsal striatum) maintains information about the rewarding outcomes of actions in order to enable better ones to be chosen more frequently (O'Doherty et al., 2004). Still, in animals midbrain dopamine neurons in substantia nigra and the VTA have recently also been shown to respond to a large category of salient and arousing events, which not only included appetitive stimuli (e.g., primary rewards), but also aversive, high intensity and novel stimuli that had no rewarding property. In addition, dopaminergic activity was found to be suppressed not only by the omission of rewards, but also by events that were associated with reduced arousal or attenuated anticipatory excitement (cf., Horvitz, 2000 for a comprehensive overview). Redgrave et al. (1999a) and Horvitz (2000) have hence suggested that, instead of being restricted to reward-related processing, mesolimbocortical and nigrostriatal dopamine neurons represent an essential component in the process of switching attentional and behavioral selections to unexpected behaviorally significant stimuli in general. Dopamine signaling is hence believed to prepare the organism for the appropriate reaction to salient environmental changes and thereby contributes to the successful execution of goal-directed behavior (cf., Horvitz, 2000). Similarly, in humans dopamine target sites in the striatum (i.e., nucleus accumbens and caudate) have also been found to be involved in representing stimulus saliency *per se* (i.e., in the representation of unrewarded salient visual distractors that had to be ignored; Zink et al., 2003).

However, this general processing function, that applies for all kinds of salient or arousing events, also implicates that neither dopamine neurons nor the striatum are actually qualified to provide information on the actual motivational significance of events (cf., Horvitz, 2000), which is however required for an adaptive behavioral choice. Horvitz (2002) has recently proposed that, instead of signaling the motivational value of salient events themselves, dopamine simply gates the throughput of orbitofrontal and amygdaloid glutamatergic inputs to dorsal and ventral striatal target regions, like it also gates the throughput of corticostriatal sensory and motor signals that are needed for correct response execution. Since, one important function of the **OFC** and **amygdala** has been found to be the representation of current reward value of environmental stimuli in humans (e.g.,

O'Doherty et al., 2000; Gottfried et al., 2003), inputs from these structures supposedly deliver decisive evaluative information about motivation-related events in the environment which then allows for adequate behavioral decisions (cf., Horvitz, 2002). Within the "motivational network" the orbitofrontal cortex and partly also the amygdala have thereby been assigned a central role in multimodal reinforcer-representation and coding of predictive reward value (e.g., Zalla et al., 2000; O'Doherty et al., 2001; Elliott et al., 2003; Elliott et al., 2004). On this account it may also be assumed, that the OFC – apart from the amygdala – constitutes the central neural source that flexibly codes information on the current and predictive motivational value of environmental stimuli. For a further understanding of this essential role in the processing of incentive and motivational value, the next section provides a more detailed overview on orbitofrontal function.

3. The orbitofrontal cortex and its role in the processing of biologically significant stimuli

Among neocortical regions the OFC has been of major interest when it comes to the representation of reward-related information (for recent reviews on orbitofrontal functioning please see: Kringelbach & Rolls, 2004; Rolls, 2004; Kringelbach, 2005). This section will provide a comprehensive overview on past and present findings regarding the functional role of the OFC in both reward processing and the processing of salient motivationally significant environmental stimuli in general whereby the emphasis will be on neuroimaging findings in humans. Since a fundamental understanding of the functional role of the OFC requires a basic knowledge on its major projections (i.e., its neural inputs and outputs), a brief outline on its most important projections – mainly derived from research on non-human primates – is further given.

3.1 Neuroanatomical connectivity of the OFC

In contrast to other prefrontal regions the OFC receives projections from the magnocellular medial part of the mediodorsal nucleus of the thalamus (cf., Fuster,

1997) and is for that reason the only prefrontal region that obtains inputs from all sensory modalities – including all "what" processing systems (e.g., the ventral visual stream) as well as visceral projections – making it the most polymodal region of the entire cortex (cf., Rolls, 1999; Rolls & Deco, 2002). It contains the secondary taste cortex and both the secondary and tertiary olfactory cortices in which not only the identity, but also the reward value of odors is represented (cf., Rolls, 2004). Due to these neuronanatomical preconditions the OFC is predisposed for multi-modal stimulus-reinforcement association learning (cf., Rolls 1999; Rolls, 2004) and may also function a crucial sensory-visceromotor link for consummatory behavior (cf., Öngür & Price, 2000).

Apart from sensory connections the OFC further has reciprocal connections with other regions that have been reported to be involved in both emotional processing and goal-directed behavior. Accordingly, the OFC has connections with the amygdala (Carmichael & Price, 1995; Cavada et al., 2000), the anterior and posterior cingulate cortices (Van Hoesen et al., 1993; Öngür & Price, 2000) also including the cingulate motor area (Cavada et al., 2000;) as well as other prefrontal regions (Barbas & Pandya, 1989; Carmichael & Price, 1995). With respect to intrinsic corticocortical connections the OFC may be divided into two networks of which one is restricted to orbital areas, while the other one involves the medial frontal cortex and orbital areas (cf., Öngür & Price, 2000). The "orbital prefrontal network" includes most areas within posterior, central and lateral orbital surface and therefore receives its major inputs from several sensory modalities and is assumed to be involved in sensory integration. In contrast, the "medial prefrontal network", which consists of all areas on the medial wall and related areas in the OFC, rather seems to provide the visceromotor link, as it provides most of the descending projections to the hypothalamus and brainstem. Connections between the two networks within the OFC provide a further basis for sensory-motor linkage (cf., Öngür & Price, 2000). Additional support for the orbitofrontal role in emotional processing comes from the observation of strong reciprocal connections with the periaqueductal gray (Rempel-Clower & Barbas, 1998) and – even more importantly – with the anterior and ventromedial striatum, thereby mainly the caudate nucleus (Eblen & Graybiel, 1995). According to Rolls (1999) this pathway could be directly involved in goal-directed behavior and may further control the dopaminergic neurons of substantia nigra pars compacta. In line with this finding there is also evidence of other pathways to

dopaminergic parts of the midbrain (Öngür & Price, 1998) and the nucleus accumbens (Haber et al., 1995). Regarding the assumed orbitofrontal influence on goal-directed motor behavior, reciprocal connections from lateral and caudal OFC to the premotor area F5, an area representing both distal arm movements through neurons that are responsive to goal-directed motor acts and motivational visual stimuli (Rizzolatti et al., 1988), have been also detected (Barbas & Pandya, 1989). Moreover, caudal OFC receives projections from the insula cortex, which relay taste, olfactory, visceral and somatosensory information (Mesulam & Mufson, 1982). Finally, the medial OFC also obtains direct ipsilateral projections from the hippocampus (Cavada et al., 2000) which may even point to an orbitofrontal involvement in memory processes, an assumption which has found converging support in some recent studies (e.g., Frey & Petrides 2002, 2003; Rolls et al., 2005).

3.2 Evidence from neuroimaging

Functional neuroimaging studies have provided evidence that points to a crucial role for the OFC in the flexible representation of primary rewards and punishments (i.e., congenital reinforcers like food) and in goal-directed behavior that is based on the rewarding properties of environmental events (cf., Kringelbach & Rolls, 2004).

3.2.1 Representation of primary and secondary reinforcers

The representation of primary reinforcers in the OFC is mainly based on the representation of the identity or intensity of sensory stimuli independent of their hedonic value (i.e., sensory integration). This could be for example the sheer taste of a food item (De Araujo et al., 2003a; Kringelbach et al., 2003) or its odor (Francis et al., 1999; De Araujo et al., 2003a). Such identity-specific activations have been preferentially detected in those orbitofrontal subareas that receive direct projections from the respective sensory modalities (e.g., the taste-sensitive activations were observed in caudal OFC that is continuous with the anterior agranular insular cortex which – together with the frontal operculum – forms the primary taste cortex; De Araujo et al., 2003a; Kringelbach et al., 2003). Moreover, taste-odor associations and

therefore flavor perception also converge in medial OFC (De Araujo, 2003a; see also: Öngür & Price, 2000), which underlines the important role of the OFC in stimulus-stimulus and stimulus-reinforcer association learning (e.g., Gottfried et al. 2003; Tabbert et al., 2005). Accordingly, secondary reinforcers, which are understood as acquired forms of reward (e.g., money) because they gained their rewarding value through the association with a primary reward, are also represented in the OFC (cf., Kringelbach & Rolls, 2004).

3.2.2 Representation of relative reward value

However, the mere identity or intensity of a primary or secondary reinforcer does not suffice for an adaptive behavioral decision. Internal needs (e.g., perceived hunger), behavioral goals and external demands (e.g., the effort associated with actual reward acquisition) have to also be taken into account. The OFC is assumed to provide the collective currency for adaptive behavioral decisions in terms of a predictive reward value (cf., Montague & Berns, 2002; Kringelbach, 2005). Observations made in reinforcer devaluation studies have shown that the OFC responds less to a food-associated odor when the respective food was eaten to satiety (Gottfried et al., 2003). In addition, reduced pleasantness ratings for a food eaten to satiety (O'Doherty et al., 2000), for liquid food-stimuli (e.g., tomato juice) in different satiety states (Kringelbach et al., 2003) and the subjective decrease in pleasantness ratings for mineral water in thirsty satiated compared to thirsty individuals (De Araujo et al., 2003b) were similarly linked to a decline in the overall orbitofrontal response. A correlation between subjective hunger ratings and orbitofrontal response was also observed during food item presentation (Morris & Dolan, 2001). These findings strongly support the assumption that the OFC tracks the perceived (subjective) reward value of primary reinforcers, which also allows for adaptive preference judgments with respect to different reward options. Coding of predictive reward value in an orbitofrontal neuron was indeed observed to parallel behavioral choice. Tremblay & Schultz (1999) reported that a monkey, having the choice between reward A and B, would choose A which was accompanied by an increased orbitofrontal response to reward A. Instead, in the concurrent presentation of reward B and C, reward B was preferentially chosen, which was also paralleled by an

increased orbitofrontal response to reward B. That means that although reward B was physically identical in both situations, its motivational value was calculated in a relative way and differed according to the other available reward in terms of the monkey's relative subjective preference.

3.2.3 Representation of flexible reward monitoring and reversal-learning

Associations formed in the OFC are never static. In contrast to the phylogenetically older amygdala, which has been reported to also code relative value (see above), but which tends to need many experimental trials before a response or an association is reversed after change in contingency, OFC appears to code (reward) reversals extremely rapidly (Rolls et al., 1996; Morris & Dolan, 2004) and further rapidly implements the new formation of a stimulus-reward association (cf., Rolls, 1999). This orbitofrontal function has been interpreted in terms of a behavioral advantage that allows for an immediate behavioral change (e.g., the escape from aversive stimuli) and is also thought to improve social abilities (e.g., through the rapid identification of changes in facial expressions). Accordingly, in a reversal-learning task the human OFC was found to be sensitive to changes in facial expression upon which a rapid behavioral change had to be executed (Kringelbach & Rolls, 2003). In the reversal-learning paradigm, subjects are commonly required to constantly monitor the (reward) outcome associated with two stimuli. The overall goal of the task is to select that one of the two stimuli that is followed by the predicted outcome (e.g., a positive reward feedback) as much as possible. However, over time stimulus-outcome contingencies change and the alternative stimulus is now associated with the desired outcome which requires a behavioral switch in stimulus choice. Accordingly, in the common reversal-learning paradigm behavioral switching should follow the first error in predicted outcome as a reliable signal that indicates that the alternative stimulus is now associated with a reward. Conversely, in a probabilistic reward-reversal-learning paradigm reward feedback is not fully predictive and not always contingent on performance. However, this paradigm has the decisive advantage, that neural responses related to punishment *per se* can be dissociated from those to punishing events that are followed by the actual behavioral change. In this context, the lateral OFC has been found to be especially responsive to punishment

leading to behavioral change (O'Doherty et al., 2001, 2003; Cools et al., 2002), which underlines its important role in the flexible representation of action-outcome associations, but further indicates that the lateral OFC may also represent inhibitory control processes that help to breach perseverative responding (Elliott & Deakin, 2005).

In addition, the OFC has also been observed to provide a powerful learning signal that depends on the discrepancy between the predicted and the actually received reward (in the sense of a reward prediction error; Ramnani et al., 2004; Tobler et al., 2006), which supposedly further strengthens behavioral responses to a stimulus that is associated with the maximal positive outcome. Accordingly, in humans orbitofrontal activity was always associated with the positive prediction error (i.e., the occurrence of an unpredicted reward), while orbitofrontal deactivations followed the unpredicted omission of an expected reward associated with a conditioned stimulus (Ramnani et al., 2004; Tobler et al., 2006). This again emphasizes the importance of the OFC in both developing flexible reward predictions based on expectations that are tied to conditioned stimuli and decision-making that is mainly guided by external cues and their expected motivational value.

3.2.4 Regional-specific processing of different aspects of biologically significant stimuli within OFC

It is also worth mentioning that some neuroimaging studies found a functional segregation within human OFC. Punishment leading to behavioral change has been reported to be preferentially represented by lateral parts, while medial OFC has been rather assumed to subserve monitoring of reward value (O'Doherty et al., 2001, 2003). A recent meta-analysis based on the results from 87 neuroimaging studies confirmed the medio-lateral trend within OFC (Kringelbach & Rolls, 2004; see also: Fig. 1, p. 21). In addition, an anterior-posterior trend was also detected within the OFC according to which an increasing complexity of the representation and processing of rewards and punishers was mirrored by the location of activation along the posterior-anterior axis. While anterior parts of the OFC were rather activated by combinations of sensory inputs (e.g., flavor) and more abstract forms of secondary reinforcers (e.g., subjective pleasantness, loss of money), posterior parts of the OFC,
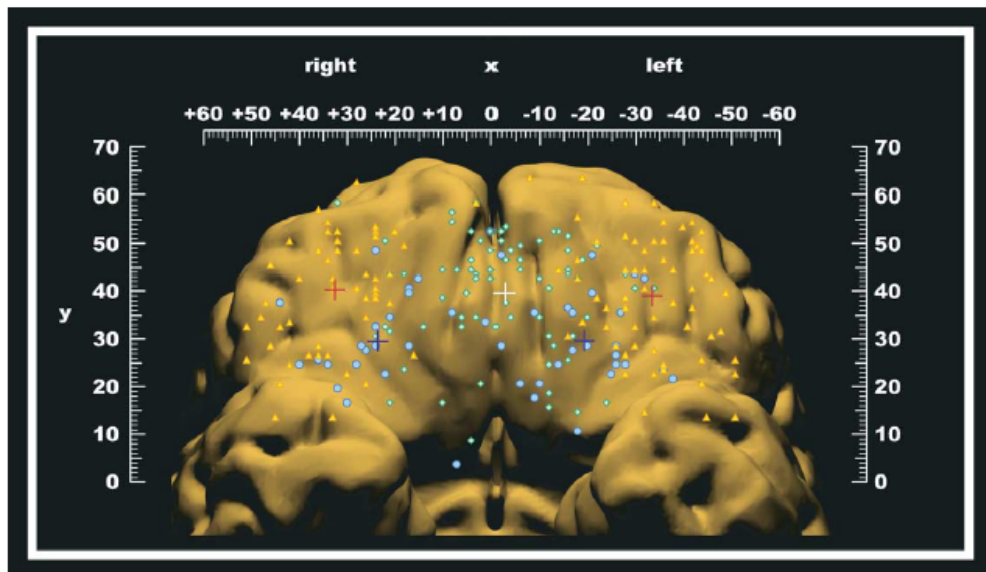
Figure 1: Activations from studies reviewed in the meta-analysis by Kringelbach & Rolls (2004). Two centers of mass of the clusters of activations related to motivation-independent reinforcer representation (blue circles) were marked with a blue cross. Similarly, punishers leading to behavioral change (yellow triangles) showed two centers of mass (red crosses). Monitoring of reward value (light green diamonds) exhibited only one center of mass (white cross). Clusters were significantly separated in a medial–lateral and anterior–posterior trend (Fig. 1 was taken from Kringelbach & Rolls, 2004).

including five-layered agranular regions, were mainly involved in processing of primary rewards and punishers which has been interpreted in terms of a processing hierarchy (Kringelbach & Rolls, 2004).

3.3 Evidence from lesion studies

From the first reported and therefore supposedly most famous case of Phineas Gage (cf., Macmillan, 2000), who survived an orbitofrontal damage caused by a metal rod penetrating the medial (orbito-)frontal cortex through the left cheek bone to the top of the head, to recent studies on patients with orbitofrontal damage (e.g., Hornak et al., 2004) the lesion-approach has helped to further elucidate the important role of the OFC in emotional processing, appropriate decision-making and social conduct.

3.3.1 Deficits in reward monitoring and reversal-learning

Most of the deficits found in patients with orbitofrontal damage can be ascribed to a disturbed integration of reward- and/ or emotion-related information (e.g., deficient evaluation of reward magnitude and changes in reward value), which also affects

behavioral decisions (cf., Rolls, 2004; Kringelbach & Rolls, 2004). For instance, social interaction has been found to be disturbed by a considerable deficit in the correct identification of emotional face or voice expression often following bilateral orbitofrontal lesions (Hornak et al., 2003). In addition, the ability to switch or reverse the choice of a certain stimulus based on its changing reward value in reward-reversal paradigms has also been shown to be impaired following bilateral ventromedial damage (e.g., Rolls et al., 1994; Freedman et al., 1998; Fellows & Farah, 2003). Recent findings thereby revealed, that this deficit cannot be attributed to a simple form of motor response inhibition or perseveration, but has been instead assumed to be caused by an impaired reward monitoring function guiding adaptive behavior (Hornak et al., 2004).

3.4 The orbitofrontal cortex and processing of salient behaviorally relevant events - Beyond the context of reward processing

Outside of the context of reward processing, the orbitofrontal involvement in the processing salient events is mostly unexplored in humans. Only a handful of neuroimaging studies – most of them using the method of positron emission tomography [Abbr. PET] – have reported an orbitofrontal response to salient events independent from reward processing. For example, in a prior functional magnetic resonance imaging [Abbr. fMRI] study from my laboratory (Gruber et al., 2006, in prep.) it has already been shown that a behaviorally relevant infrequent stimulus attribute, which required subjects to rapidly adjust their behavior towards the infrequent and therefore salient change – amongst other regions – activated parts of the posterior OFC. Increased posterior orbitofrontal activation has also been found in response to the detection of unexpected salient visual stimuli which strongly deviated from expectation (Petrides et al., 2002), in association with unexpected unpleasant sounds (Frey et al., 2000), during selection of currently relevant memories (Schnider et al., 2000; Treyer et al., 2003) or in a guessing task with an uncertain outcome (Schnider et al., 2005). More anterior parts of the OFC were further involved in the representation of rarely occurring invalid spatial or temporal cues (Nobre et al., 1999) and in general outcome monitoring processes independent from reward processing (Schnider et al., 2005; see also: Fig. 3, p. 28).

Even though each of the above-mentioned studies found reliable activations within the OFC, none of them had provided subjects with reward or any other special incentive for correct performance. Instead, these studies simply used experimental manipulations that included stimuli, which were both highly salient (e.g., unpleasant or infrequent) and also somehow relevant for current or future behavior. For instance, in the previous study from my laboratory (Gruber et al., 2006, in prep.) subjects were given a simple verbal instruction, which made an infrequent stimulus attribute (i.e., the color white) behaviorally relevant and therefore a prospective behavioral goal. In the rare case of its occurrence in the shape task, subjects had to disregard the shape dimension and execute an alternative button press in the shape task. Interestingly, a region in the posterior OFC was exclusively activated in that particular situational context, in which the stimulus attribute was both infrequent and behaviorally relevant, but not if an infrequent but actually irrelevant stimulus attribute was presented that had to be ignored (i.e., in a situation of infrequency *per se*) or when the deviant color was presented frequently in a separate session, but still required the same alternative button press (i.e., in a situation of mere behavioral relevance).

In addition, some other studies which used stimuli with varying reward- and punishment-levels also led to the inference that the posterior part of the OFC was less involved in the representation of the positive valence of rewarded events, but rather showed a valence-independent coding of emotional salience in general. Accordingly, both winning in the context of a winning-streak and a penalty in the context of a big loss led to a reliable activation within posterior OFC (Elliott et al., 2000a). A similar activation has been observed when it came to the best or the worst outcome out of a range of possible rewards (Breiter et al., 2001; Elliott et al., 2003), indicating that it was rather the subjectively perceived (behavioral) significance of the event, which activated the posterior OFC, than the actual hedonic value of the respective outcome (see also: Fig. 3, p. 28).

In sum, the above described findings allow for the inference that posterior OFC responded in a context-sensitive way to those stimuli that were maximally salient and also behaviorally relevant regardless of their actual valence, which argues for a more general role of the OFC in processing of salient meaningful events outside of the context of reward processing (cf., second working hypothesis, p. 30). Nevertheless,

not every infrequent and response-relevant event previously activated the OFC. The next section will address this issue and will further derive an explanation.

3.4.1 The neural correlates of salience processing in the oddball paradigm and the OFC

Apart from the studies described above, a systematic manipulation of the salience and behavioral relevance of experimental stimuli has also been achieved by manipulating the frequency or familiarity of either task-relevant or irrelevant stimuli. In the classical oddball paradigm, response-relevant (infrequent) oddball targets were randomly presented within a stream of frequent standard stimuli within one attended modality (e.g., the visual modality). While the standard stimuli in most previous studies required no response, targets were behaviorally relevant and either had to be counted or necessitated a manual response. In some studies presentation of infrequent response-relevant targets was also accompanied by randomly interspersed infrequent distractors or non-repeating novel stimuli, which – like the frequent standard stimuli – also required no response (e.g., McCarthy et al., 1997; Menon et al., 1997; Casey et al., 2001; Bledowski et al., 2004). Another variant of this paradigm required subjects to process two modalities (e.g., auditory and visual stimuli) at the same time, of which only one contained response-relevant targets and had to be attended for stimulus changes, while the other modality was processed outside of the focus of attention and stimulus-changes had to be ignored (e.g., Downar et al., 2001). Still, what most variants of the oddball-paradigm had in common was, that only the oddball-targets entailed a voluntary response initiation, while all other events had to be ignored. Auditory, visual and tactile processing has been similarly addressed by oddball studies. For that reason, there exists a comprehensive research record on brain regions that have been generally found to be involved in the processing of salient events that could either be task relevant or irrelevant. Interestingly, the variants of the oddball-paradigm activated roughly the same regions (e.g., Downar et al., 2001; Bledowski et al., 2004; Kiehl et al., 2005a), whereby task-relevant events have mostly been found to elicit overall stronger responses (Downar et al., 2001) and sometimes even selective responses (Clark et al., 2000). In all up to about 40 regions have been found to be activated by different
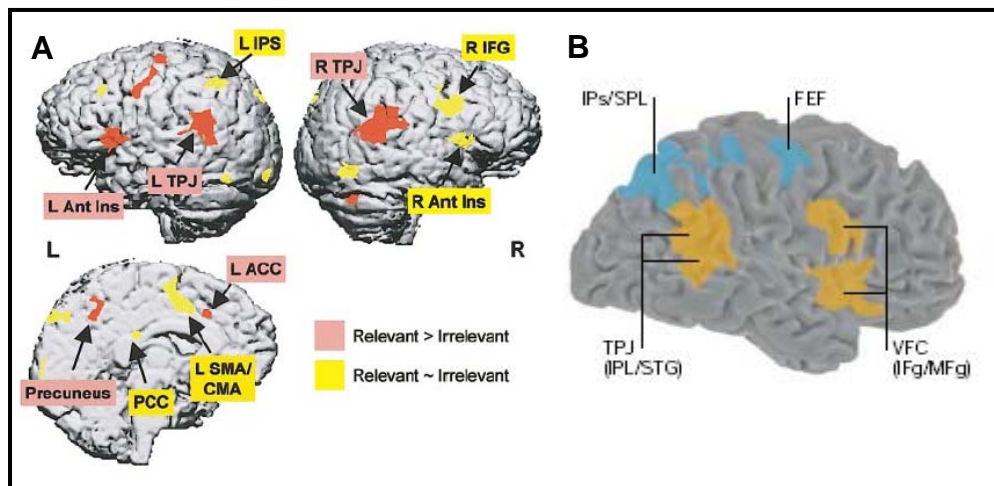
Figure 2: Regions commonly observed in target-detection in the oddball paradigm. (A) <u>in red</u>: regions that were more responsive to task-relevant stimuli; <u>in yellow</u>: regions that were equally responsive to both task-relevant and irrelevant stimuli (Fig. 2A was taken from Downar et al., 2001). (B) Dorsal and ventral fronto-parietal networks involved in attentional control processes. The dorsal network is displayed <u>in blue</u>, the ventral one, which is assumed to be important in detection of salient behaviorally relevant stimuli, appears <u>in yellow</u> (Fig. 2B was taken from Corbetta & Shulman, 2002).

types of salient events (i.e., targets, distractors and novels) presented in the oddball paradigm, which were consistently observed in both the auditory, visual and tactile modality and occurred similarly across gender and age (Kiehl et al., 2005a). Among them were the temporoparietal junction [Abbr. TPJ], which comprises the posterior superior temporal gyrus and adjacent parts of the supramarginal gyrus, the intraparietal lobe, superior and middle frontal gyri, inferior frontal gyrus and anterior insular cortex as well as anterior cingulate and the supplementary motor area [Abbr. SMA] (cf., Fig. 2A, this page). Especially the TPJ has been assigned the decisive role within a general alerting system, which also includes parts of the inferior frontal cortex (cf., Corbetta & Shulman, 2002; see also: Fig. 2B, this page). This ventral frontoparietal system has been assumed to provide a reflexive circuit-breaking function that is thought to interrupt ongoing goal-directed cognitive activity in dorsal frontoparietal areas (i.e., the intraparietal and superior frontal cortex) upon detection of salient events, especially when the salient event is considered as behaviorally relevant, and may therefore be assumed to be an important neural correlate if stimulus salience. Still, the individual roles of most of the remaining regions observed within the framework of deviance detection in the oddball paradigm remain to be elucidated. To date it is not even clear whether all of these regions are actually necessary for successful task performance in the oddball-paradigm. Halgren and Marinkovich (1996) proposed that the brain appears to adopt a strategy of engaging many potentially useful brain regions despite the low probability that these regions are actually necessary, which might however facilitate incidental learning,

performance monitoring or contextual updating. This assumption has been supported by observations made in subjects with focal lesions affecting some of the above described regions, who were, despite circumscribed brain damage, still able to detect target stimuli (e.g., Daffner et al., 2000). Nevertheless, the actual process of engaging the distributed neuronal system has also been assumed to be reflexive and occurs when the eliciting stimulus is salient, either due to its novelty or by manipulating top–down processes like making it task-relevant (Kiehl et al., 2005a), which has been termed "adaptive reflexive processing" (Kiehl et al., 2005a, pp. 899, 910).

So far, only a minority of oddball-studies reported orbitofrontal activity in response to salient behaviorally relevant events (i.e., oddball-targets). For instance, one study, dealing with olfactory change detection in a common oddball paradigm, reported central OFC activity in association with the presentation of unexpected odor-deviants (Sabri et al., 2005). Conversely, attended odor-deviants, which had to be counted by the participants, activated right anterior OFC (Sabri et al., 2005). In addition, Clark et al. (2001) found an orbitofrontal response in association with rare visual distractor stimuli. Conversely, another study using visual stimuli observed a contrasting activation pattern showing that the activation in the ventral prefrontal cortex – also including the OFC – increased when participants processed high-frequency targets, while decreasing target frequency led to a significant decline in activation (Casey et al., 2001). These partly contrasting findings imply that the OFC may not be considered as an essential part of the "adaptive reflexive processing network", but only comes into play when either goal-related changes or specific manipulations within the task (e.g., stimulus changes within the olfactory modality) necessitate an orbitofrontal involvement. As already has been outlined above, the OFC has been assumed to be especially involved in the implementation of rapid changes in goal-directed behavior and the reversal of stimulus-response associations. In the above described study from my laboratory, which reported a posterior orbitofrontal activation in association with a behaviorally relevant infrequent target event, Gruber et al. (2006, in prep.) used a deviant color as a prospective memory target that was presented exclusively in the shape task. This meant, that subjects had actually prepared the stimulus-response mapping of the shape task and had to rapidly adjust their behavioral goal (and also reverse the stimulus-response association) towards the infrequent target event presented in the currently irrelevant stimulus dimension color.

In contrast, the common oddball task simply requires subjects to make a yes-no decision (i.e., press target button if target stimulus appears and withhold response if a stimulus other than a target is detected). For that reason, in the oddball task the best strategy may be, to simply focus on infrequent target appearance, while ignoring the remaining frequently occurring standard and infrequently presented distractor or novel events. Thus, the oddball task does not necessitate a reversal of the actual behavioral goal (target-detection) and the associated response, because the infrequent targets always require an identical response and the behavioral goal never changes throughout the task, which means, that even though the oddball paradigm includes salient events (i.e., unpredicted infrequent events), these events are not behaviorally relevant in the sense, that they require an actual context-sensitive adjustment of behavior. Instead, the oddball paradigm measures the inidvidual's response initiation ability to target events that are presented infrequently and therefore commonly does not lead to an activation of the (posterior) OFC.

4. Rationale of the present study

The introduction largely dealt with orbitofrontal function within the framework of reward processing and motivated behavior. It further highlighted the important role of the OFC in flexible coding of relative reward value and rapid reversal-learning, giving us a hint as to how the OFC implements context-sensitive and adaptive decision-making. In addition, the introduction also illustrated that the OFC cannot be assumed to be exclusively responsive to rewarding events, as this cortical region exhibited significant responses to other salient behaviorally relevant events. For instance, low-frequency events that required an adjustment in goal-directed behavior have been shown to activate the posterior OFC (Gruber et al., 2006, in prep.; see also: Fig. 3A, p. 28). Interestingly, similar parts of the posterior OFC have been also implicated in context-dependent reward processing (Elliott et al., 2000a; Morris & Dolan, 2001; Gottfried et al. 2003; see also: Fig. 3F, 3C, 3B, p. 28), processing of motivationally meaningful events, regardless of their actual valence (Breiter et al., 2001; Elliott et al.; 2003; see also: Fig. 3E, p. 28), as well as other forms of arousing stimuli without a reward association (e.g., Petrides et al., 2002; Schnider et al., 2005;
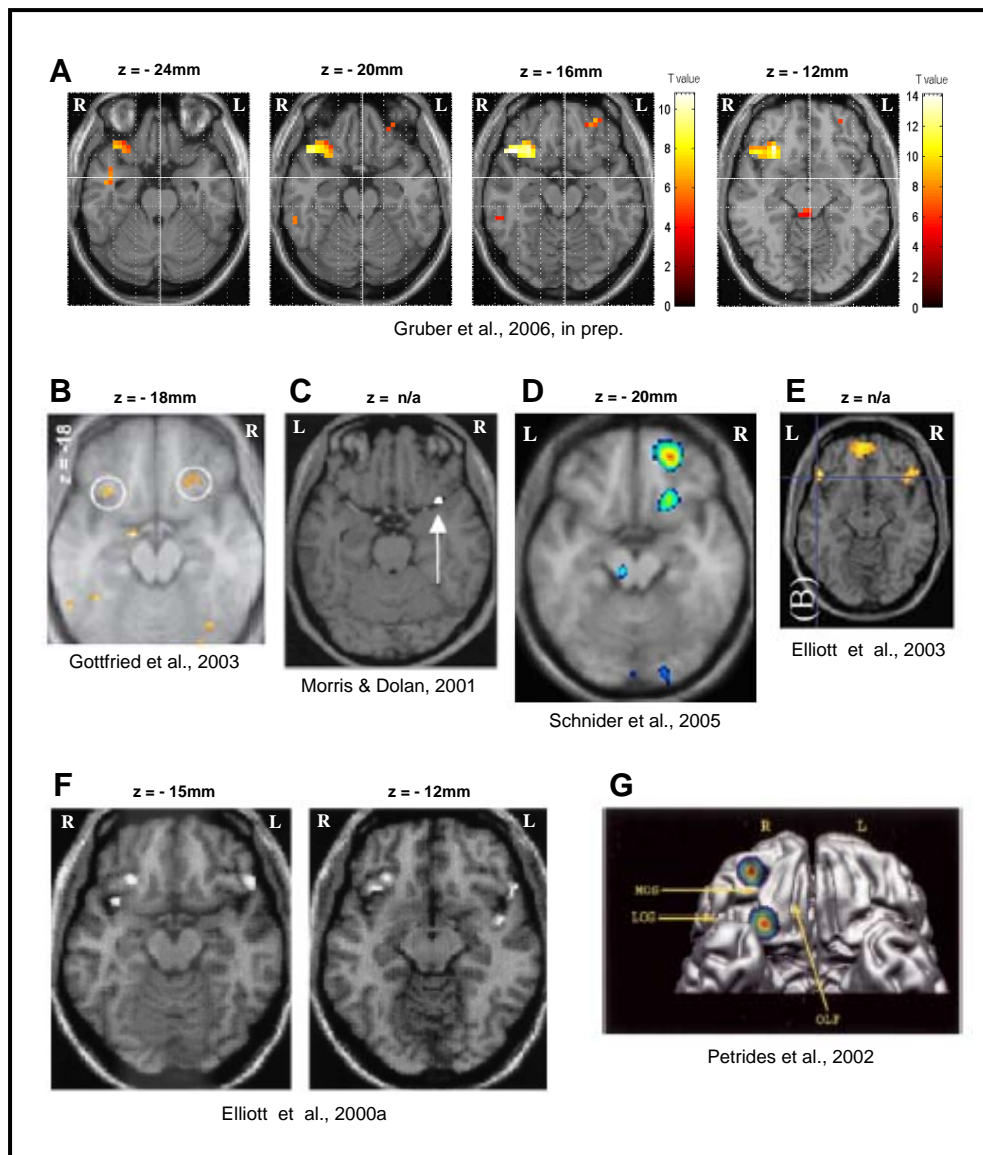
Figure 3: A selection of studies showing posterior orbitofrontal activations in association with different forms of salient (behaviorally relevant) events. (A) evoked by infrequent behaviorally relevant events that required a behavioral adjustment displayed on the MNI-template in radiological convention [Abbr. RC]; (B) sensitive to reinforcer devaluation by satiety; MNI-template in neurological convention [Abbr. NC]; (C) positive correlation with subjective hunger ratings; representative subject, in NC; (D) evoked by uncertainty during guessing; MNI-template, in NC; (E) responsive to both highest and lowest reward value; n/a, in NC; (F) activated during both reward in a winning streak and penalty during increasing loss; standard MRI-template (n/a), in RC; (G) activated by deviance detection; displayed on a reconstruction of ventral brain surface. All figures were taken from the respective study indicated below the particular figure.

see also: Fig. 3G & 3D, this page). In line with these prior observations, in the present study it was hypothesized that the posterior OFC subserves a neural mechanism that is involved in the evaluation and identification of salient behaviorally relevant events in general, which does not emerge exclusively in the context of reward and positive reinforcement, but whenever a salient event occurs, that is also behaviorally relevant. This mechanism would allow for the rapid adjustment of behavior towards or away from all kinds of behaviorally relevant or motivationally significant salient events and would probably guarantee behavioral

flexibility, which ensures survival. Accordingly, the present thesis was intended to disentangle whether rewards and other forms of salient behaviorally relevant events are processed by an identical subarea of the OFC (i.e., by its posterior part) or whether they are coded separately within the OFC. For that purpose, the exact nature of the behavioral relevance of experimental events was systematically varied over the course of our experiment. This allowed for a direct comparison of the neural mechanisms involved in the processing of biologically significant events that signaled the chance to gain a reward, with neural responses to low-frequency events (i.e., oddballs) that required an adaptation of motor-behavior (in form of a button-press) without being rewarded. To my knowledge, so far this is the first investigation that directly compared the orbitofrontal responses elicited by rewarded events with the orbitofrontal response to other forms of salient behaviorally relevant events presented <u>within a single study</u>.

4.1 Working hypotheses

The first but **minor goal** of this study was to replicate the imaging findings made in the previous study by Gruber et al. (2006, in prep.). This previous study had used a three-session design in which the salience (frequency) and the behavioral relevance of an oddball event (i.e., a white color in the shape task) were systematically varied over the course of three experimental sessions. Accordingly, the presented visual oddballs were either infrequent, but irrelevant for the behavioral response to be given and had to be ignored (in session 1), infrequent and behaviorally relevant (in session 2) or frequent and behaviorally relevant (in session 3).

The current study was intended to replicate the orbitofrontal activation that had occurred exclusively in the context of session 2 by making use of a one-session design (see below). Such a one-session design had the advantage that irrelevant and behaviorally relevant infrequent oddballs were presented together in the same session, which ruled out the possibility that the orbitofrontal activation, which had been detected in session 2 of the previous study, may be simply explained by a reversal-learning process taking place when subjects had to change the behavior from session 1, in which the white color had to be ignored, to session 2, in which the same

white oddball event became a prospective memory target that was also response relevant.

The **first working hypothesis** (1) therefore was:

> (1)   Behaviorally relevant infrequent oddballs induce a significant increase in orbitofrontal activity.

The second but **major goal** of this study was to examine whether the posterior OFC subserves a general function in the processing of salient behaviorally relevant events. The prediction was that events with a positive reward association and other behaviorally relevant salient events, that required a behavioral adjustment, but lacked an association with a reward, would be represented by an identical orbitofrontal subarea (see above described rationale of the study). This prediction led to the **second and major working hypothesis** (2) and its respective alternative (2A):

> (2)   Both forms of behaviorally relevant events (i.e., infrequent events that require a behavioral adjustment and events with a reward association) induce a significant increase in activation within an identical orbitofrontal subarea.

> (2A) Both forms of behaviorally relevant events are coded separately within the OFC.

In the following section the methodological background of the current study will be outlined. In this section it will be also explained why the respective methods were preferentially chosen to test the above-named hypotheses.

IV. Material and Methods

1. A brief introduction to the principles of (functional) magnetic resonance imaging

Magnetic resonance arises from the interaction of an applied magnetic field with nuclei having a magnetic moment. Atomic nuclei (e.g., ^{1}H) with a nuclear spin (i.e., the basic feature of elementary particles rotating about their center) can behave as simple magnetic dipoles, which can assume either a high-energy state (i.e., behaving as if they are oriented against the applied field) or a low-energy state (i.e., oriented with the applied magnetic field). Transitions between the two energy states are accompanied by an absorption or an emission of energy in the radiofrequency range. Since the frequency of the energy emitted by an excited nucleus is proportional to the magnetic field experienced and the precise relation between the resonance frequency and the applied magnetic field differs for individual nuclei, magnetic resonance imaging systems can be calibrated to detect specific types of nuclei. The spatial localization of resonating nuclei is achieved through the application of small magnetic field gradients. These gradients are superimposed on a larger homogeneous static magnetic field of the imaging magnet of the scanner. Differences in resonance frequency (and also phase) of nuclei allow the measurement of the relative positions of molecules along the smaller gradient field. This is possible, because the resonance frequency of a nucleus in a compound is proportional to the applied field strength (see above), which in this case is represented by the sum of the large static field of the magnet and the smaller field of the gradient coil (cf., Jezzard & Clare, 2002; Matthews, 2002; Weishaupt et al., 2006).

The image contrast generated in MRI – and therefore the brain components highlighted in the actual image – depends on the relaxation time measured. After an excitation pulse the spins of the excited protons rotate in the XY-plane, which is called transversal magnetization. This causes the MR-signal. There are two independent processes which lead to a reduction in the magnetization and the MR-signal until the initial state before excitation is actually reached. While T1 is called the longitudinal relaxation time which results from spins that emit energy to the environment to return to their original orientation (i.e., become aligned with the longitudinal direction of the static magnetic field), T2 and T2* are independent

components of the transversal relaxation time, which are characterized by a loss of transversal magnetization resulting from the spins becoming out-of-phase. The T2 relaxation time is the component, which is characterized by a spin-spin-interaction independent from the strength of the magnetic field. In this case spins become out-of-phase due to changes in their precession caused by the interaction with other spins. The T2* relaxation time however depends on constant inhomogeneities of the applied static magnetic field caused by the scanner and the human body, leading to dephasing of spins. In sum, the T1 relaxation time of a certain kind of tissue determines how fast nuclear spins "recover" from the excitation, while the T2 and the T2* relaxation time mainly define how fast the MR-signal and therefore the transverse magnetization decays after excitation. What actually formed the basis for the functional images acquired in the current fMRI study was the so called Blood Oxygenation Level Dependent [Abbr. BOLD] response which is based on a contrast that arises from changes in the local "magnetic susceptibility" (i.e., the distortion of the applied magnetic field exerted by the interaction with a material). The 'material' leading to this distortion was the degree to which hemoglobin was deoxygenated (cf., Jezzard & Clare, 2002; Matthews, 2002; Weishaupt et al., 2003). In the next section the physiological and physical processes causing the BOLD signal will be described in further detail.

1.1 The physiological basis of the BOLD signal

In the brain one way of information processing is through axons, which transfer information by electrical conduction (through action potentials). The action potential triggers the release of neurotransmitters at synapses. These neurotransmitter molecules then interact with specific receptors on the post-synaptic target neuron, which leads to changes in the membrane potential and alters depolarisation frequency either making the neuron more sensitive (excitatory effect) or nonsensitive (inhibitory effect) for an action potential (cf., Thompson, 2001). Neurotransmitter release is accompanied by metabolic changes in neurons and glia cells that require a certain amount of energy used around or in the synapses. Energy production comes along with a greater local demand for oxygen (oxidative metabolism) which also leads to an increased local blood flow (neuro-vascular coupling of cerebral blood

flow and oxygenation), which is not restricted to the site of neural activity, but occurs in a larger area. Thereby, the total increase in oxygen delivery exceeds the increase in actual oxygen utilization. Nevertheless, increases in local cerebral blood flow do not exclusively occur as a result of an increase in actual oxygen demand, but there are other interacting mechanisms also responsible for blood flow regulation in the brain (e.g., hormonal or myogenic mechanisms, cf., Matthews, 2002). For instance, some recent studies point to an important role of neurotransmitter-related signalling as driving hemodynamic responses (for a critical review please see: Attwell & Iadecola, 2002).

Regardless of this ongoing discussion on the fundamental mechanisms, thought to underlie the actual regulation of the local cerebral blood flow, it still remains the local increase in both cerebral blood flow and total oxygen delivery exceeding the increase in actual oxygen utilization which provides the basis for the imaging contrast that is measured in fMRI. The BOLD fMRI contrast arises from the ratio of oxy- to deoxyhemoglobin in local draining venules and veins that accompany neural activation (Ogawa et al., 1993; see also: Matthews, 2002). When bound to oxygen, hemoglobin has the attribute of being diamagnetic, making it a sensitive marker to the level of blood oxygenation, while deoxygenated blood has been shown to be paramagnetic due to its four unpaired electrons (Pauling & Coryell, 1936; see also: Weishaupt et al. 2003). This difference influences the magnetic flux in the respective material with the effect that magnetic flux is reduced in a diamagnetic material and increased in paramagnetic material attracting the applied magnetic field. Local distortions of a magnetic field are therefore changed by a change in hemoglobin oxygenation. A decrease in the oxygenation level of blood (which is more specifically an increase in the level of deoxyhemoglobin) leads to a variation in the magnetic field across a volume element [Abbr. voxel], which causes signal dephasing and for that reason leads to a decrease in the T2* relaxation time, resulting in slightly lower signal in a T2*-weighted image. The T2 of blood decreases also, but to a lesser extent. The reverse is true for a rising level in blood oxygenation, due to increased perfusion of oxygenated blood following neural activation, leading to a higher signal in a T2*-weighted image. The fMRI BOLD- response is a mainly positive signal change, representing a decrease in the concentration of deoxyhemoglobin and can for that reason be detected in a T2*-weighted image (cf., Jezzard & Clare, 2002; Matthews, 2002). The time course of the BOLD response in
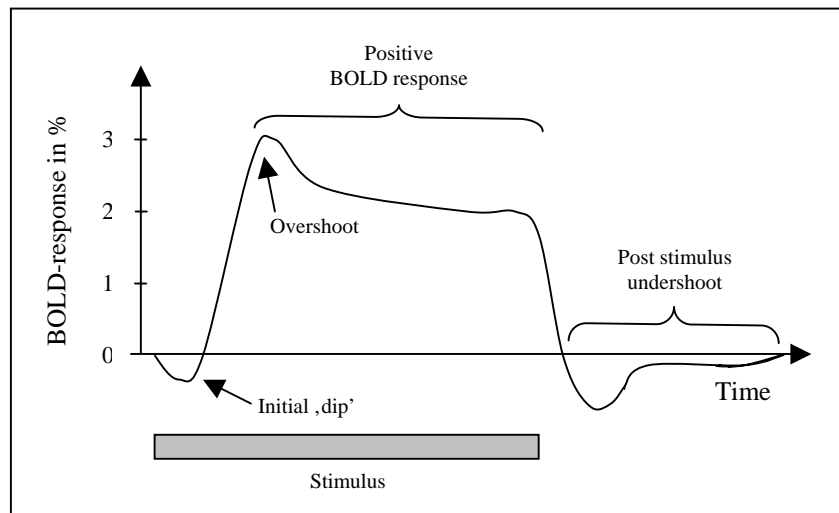
Figure 4: Schematic representation of the common features of the fMRI BOLD response to a period of neuronal stimulation (Fig. 4 was taken from Hoge & Pike, 2002).

activation is complex (cf., Fig. 4, this page). The actual increase in blood flow of about 50-70% normally occurs 2-5 s following neural stimulation and peaks at 5-8 s. The accompanying rise in the oxyhemoglobin/ deoxyhemoglobin ratio yields a robust 'positive BOLD response' in the gradient echo image (e.g., 2-3 % signal change at 1.5 Tesla). After stimulus cessation, synaptic activity decreases, which lets blood flow decay back to baseline (cf., Matthews, 2002; Hoge & Pike, 2002).

In sum, the fundamental characteristics of the BOLD fMRI response are useful for the identification of activation-related changes in gray matter and synaptic and/ or dendritic activity in particular. However, the BOLD fMRI response is mainly an indirect measure of neuronal activity even though under some circumstances there should also be a direct relationship between neuronal discharge rate and the magnitude of the BOLD response (Rees et al., 2000; see also: Matthews, 2002).

1.2 Spatial & temporal resolution in MRI

The fact that the region of blood perfusion increase may be somewhat larger and distant from the actual site of neural activity leads to limitations in spatial resolution of MR images, in that the actual spatial resolution of the MR map may not be greater than 2-3 mm. Further, due to the physiological properties of the BOLD signal (i.e., a brief neural event lasting only less than a millisecond leads to BOLD signal change which peaks after about 6 s and returns to baseline over more than 12 s), the actual

temporal resolution is also limited, even though the actual MR images can be obtained quite fast (e.g., in 10 frames per second). For that reason, deconvolution methods are needed for the differentiation of events in event-related fMRI-designs (cf., Jezzard & Clare, 2002).

1.3 Event-related fMRI

With event-related [Abbr. ER] fMRI it becomes possible to parallel behavioral studies with fMRI (cf., Rosen et al. 1998). The separation of rapidly occurring neuronal events is thereby possible, even if the hemodynamic responses they elicit overlapped, because the hemodynamic response has been shown to summate in a roughly linear fashion over time (Boynton et al. 1996; Dale & Buckner 1997). Further, it appears that the hemodynamic response is reasonably stable across subjects (e.g., 72% of the variance of the shape of one subject's response could be predicted, on average, by any other subject; Buckner et al. 1998). The huge advantage of ER-fMRI thereby is that it allows for the analysis of effects which are not stable (e.g., novelty effects) or which cannot be tested in a block-design (e.g., infrequency effects; Buckner, 1998). For that reason, ER-fMRI was the method of choice applied in the current study.

2. Data basis

This study was originally based on the fMRI-data and the behavioral data (i.e., reaction times and rates of correct responses) of 12 healthy right-handed subjects (mean age = 24.3 years; SD = 3.4 years; age range = 21 – 32 years) who had to execute a neuropsychological experiment. An equal number of female and male participants was deliberately included in order to avoid any gender-specific effects to confound with the neural response. After application of the exclusion criteria 10 subjects (5f, 5m) remained in the sample.

Before the actual neuropsychological experiment took place, two general questionnaires acquired data on medication status, intake of stimulative drugs (e.g., alcohol) prior to the investigation as well as on general contraindications for

participation in an fMRI study. This revealed that five of the six female subjects took oral contraceptives on a regular basis, while one male subject took antihistaminic treatment on the morning prior to investigation. In addition, two male subjects were smokers on a regular basis (last nicotine-consumption 2 hours and 4 hours before the investigation), while one female participant indicated that she had smoked the last cigarette 10 hours before coming to the university hospital. The latter participant also reported slight alcohol-intake on the evening prior to investigation (approximately 10 hours before arrival at the institute). Finally, three participants also reported that they drank coffee, but no less than 3 hours before coming to the lab.

The data basis was further complemented by two standard psychological questionnaires assessing different personality characteristics (see below).

3. Location and date of the study

The study was carried out on a 3-Tesla MRI Scanner (Siemens MRT Allegra; Siemens, Germany) at the Brain Imaging Center [Abbr. BIC] in Frankfurt/ Main during two days of a weekend (the 16th and 17th of July, 2005).

4. Course of examination

Subjects were recruited from an academic environment either by word of mouth advertisement or by advertisements on the blackboards of the University of Frankfurt and the Saarland University Hospital in Homburg. They were provided with an initial description of the study (i.e., course of the examination, expected duration of scanning procedure, requirements) and were further informed about the purpose of the research project. Participants were also guaranteed a general payment of €25 for participation with the additional chance to win the amount of €50 depending on their overall performance (see below: Description of the experimental paradigm). After providing subjects with this information subjects were asked whether they wanted to participate. On agreement on participation participants, gave written informed consent and were told that participation was totally voluntary and that they were free to finish the experiment at any point (e.g., when they did not feel well in the

scanner), which did not affect their final payment of € 25. Subjects were further guaranteed that the data acquired in this study would be treated confidentially according to the guidelines of data protection.

Participants were trained in the week before the experiment at a normal personal computer [Abbr. PC] outside of the scanner and also got the chance to familiarize themselves with the button box in the scanner before the actual neuropsychological experiment took place. In addition, they filled in two personality questionnaires, which are described in further detail below, and answered two general questionnaires. The first general questionnaire included questions about subjects' age, gender, handedness, coffee or alcohol consumption within 12 hours before the study, medication status (i.e., whether they took any medication on a regular basis) and whether they were smokers or non-smokers, while the second one assessed any general contra-indications for participation in an fMRI-study (e.g., metal implants, pregnancy, cardiac pace-maker). None of the 12 participants fulfilled any of the contra-indications for participation in an fMRI-study and therefore everybody was tested with the neuropsychological paradigm in the MRI-scanner. The scan started with a structural scanning sequence to get a full brain-volume of subjects' individual anatomy for approximately 8 minutes, before the actual experiment began (for a more detailed description of the scanning procedure please see below). The psychological experiment was subdivided into 3 fMRI scans and subjects had two breaks to allow for a short rest. A break lasted approximately 1 to 5 minutes and ended on subjects' demand. Besides these breaks, subjects also got the chance to press a pneumatic bulb whenever they wanted to finish the experiment. However, none of them discontinued the experiment before it actually ended.

5. Exclusion criteria

Subjects could be excluded from the study for different reasons. Firstly, any previous or prevailing mental illness did not allow for the participation in the current study. Secondly, brain injury, operation or trauma in the past also led to an immediate exclusion from the study as these events may have led to considerable tissue damage that could have interfered with the normal metabolism or blood flow in the brain and could have led to regional changes in neural responsiveness. Thirdly, during fMRI-

data acquisition in the scanner extensive head motion also led to exclusion from further analysis as motion-related artifacts could have confounded with the experimentally manipulated brain activation. Finally, subjects with error rates on more than 15% of all experimental trials also had to be excluded from further analysis, as error-related activations could have also confounded with regional brain activation.

Since the participants were recruited from the population of university undergraduate and graduate students, none of them had to be excluded for any of the first two exclusion criteria. Application of criterion three and four still led to the exclusion of two participants after scanning, who nevertheless got the full payment of € 25 for participation. One participant had to be discarded from analysis due to bad performance (i.e., errors in more than 15% of all trials), while the other person showed extraordinary head motion during the scanning procedure (more than 3mm over the course of the experiment) when compared to the other subjects.

6. Acquisition of the psychological study-parameters

The psychological examination included both a paper-and-pencil measurement with two conventional psychological questionnaires and the actual neuropsychological experiment in the MRI-scanner, which was invented for testing the two working hypotheses presented above.

6.1 Psychological Questionnaires

In order to assess subjects' personality profiles and their competitiveness two psychological questionnaires were administered in the week before the experiment. The first one was a modified German version of Cloninger's Temperament and Character Inventory [Abbr. TCI] (Richter et al., 1999), while the second one was the Competitiveness Index [Abbr. CI] by Houston et al. (1992), which was translated form English into German.

6.1.1 The Temperament and Character Inventory (TCI)

The TCI has been developed as a test, which explores inter-individual differences in the basic dimensions of temperament and character (e.g., Cloninger, 1987; Cloninger et al., 1993). The four temperament traits (i.e., novelty seeking, harm avoidance, reward dependence and persistence) have been defined as automatic emotional reactions to everyday experiences, which are considered to be heritable and appear to be relatively stable throughout life.

The trait **novelty seeking** has been characterized as underlying a behavioral activation system controlled by dopamine. This trait is therefore thought to be associated with a differential responsiveness to novel stimuli as well as a differential approach-behavior towards signals of reward and withdrawal–behavior to avoid punishment. Individuals with scores higher than average are assumed to be impulsive, quick-tempered, extravagant, and disorderly, while people with low scores are supposed to be rigid, stoical, frugal, and orderly. In contrast, the trait **harm avoidance** is the expression of the system of behavioral inhibition, which also includes reactions to reward signals and has been supposed to be mainly dominated by the serotonin system. High scores are characterized by fearful, pessimistic, shy, and fatigable behavior, low scorers are supposed to be risk-taking, optimistic, outgoing, and vigorous. The system, which has been associated with maintenance of behavior without further reinforcement and which is supposedly based on noradrenergic effects, is expressed by the traits of reward dependence and persistence. High **reward dependence** scores are presumably associated with approval seeking, whereas individuals that are low in this trait are supposed to be detached. Individuals who are high in **persistence** are characterized by being determined, perfectionist and overachievers (for a more comprehensive outline please see: Richter et al., 1999).

The general characterization of the personality profile with the TCI is based on both the dimensional and the categorical description of the individual. For personality categorization the TCI-percent-rank-values of each dimension have been divided into three groups (i.e., low = 0-33%; average = 34-66% and high = 67-100%). While individuals with either high or low values on one personality dimension are supposed to be typical in their behavioral patterns, those with near average values are rather assumed to show unstable behavioral reaction and behave rather atypical. To date a

population-validated categorization of individuals is only possible for novelty seeking, reward dependence and harm avoidance. The three traits allow for a typology that includes a flexible type together with 8 extreme types that have been proposed to represent 33% of the population (i.e., ~3.7% each), while the remaining 8 alleviated types represent 67% of the population (Richter et al., 1999). For further test-theoretical concerns (e.g., construction of TCI-scores, reliability and validity indicators, German norm-population) the interested reader may refer to the German version of the TCI (cf., Richter et al. 1999), as a more detailed description would be beyond the rationale of this thesis.

In contrast to the four temperament dimensions, the three character dimensions of the TCI (self-directedness, cooperativeness and self-transcendence) have been assumed to be rather influenced by sociocultural learning and mature throughout the life cycle. The character dimensions are important with regard to the clinical population, because they are essential for evaluating degree of maturity in the regulation of emotional conflicts (cf., Cloninger et al., 1993; Richter et al., 1999).

For the purpose of the current study, it was decided to exclusively assess the four temperament dimensions of the TCI, because the subject under investigation (i.e., the neural correlates of reactions to different forms of behaviorally relevant events) was assumed to recur on a rather basic and phylogenetically old behavioral capability that presumably recurs on the diverse behavioral and neurotransmitter systems that are supposed to underlie the overt TCI-temperament traits (i.e., the systems of behavioral activation, behavioral inhibition and persistence; see above). Inter-individual differences in temperament could therefore have represented a serious confound as temperament could have differentially affected behavioral performance and/ or the neurophysiological response in different subjects, even when performing the same experimental task. The assessment of the TCI temperament traits therefore provided the opportunity to control for strong inter-individual differences in TCI-temperament dimensions, in order to get a sample with an overall average score and would have even allowed me to exclude participants with extreme profiles, if necessary.

6.1.2 The Competitiveness Index (CI)

The CI by Houston et al. (1992) consists of 20 true-false items concerning interpersonal competitiveness in everyday social contexts and has a high internal consistency (Cronbach's alpha = 0.90). The assessment of the individual competitiveness score is based on a norm-sample of approximately 500 US-American undergraduates. Accordingly, the assumed population-mean is 9.52 (SD = 4.62) for women and 12.06 (SD = 4.88) for men, respectively. CI scores of 14 or above for women and 15 or above for men are considered as high, while low scores start at 6 for women and 7 for men.

The CI was administered to participants in order to test for inter-individual differences in competitiveness, which could have again affected behavioral effort and performance in the neuropsychological experiment.

6.2 Neuropsychological test procedure - Description of the experimental design

In the present study subjects underwent fMRI while performing a cue task switching paradigm in which they had to respond to either the color or the shape of abstract geometric objects. The paradigm was structured quite similar to the previously employed paradigm (Gruber et al., 2006, in prep.), but also included new aspects (a one-session design was employed which further also included events with a reward association).

Within the task switching paradigm two different objects were presented that appeared in one out of four different colors. The two shapes and two of the colors (i.e., the colors red and blue) were mapped to the same manual response-buttons throughout the whole experiment and could occur in both the color and the shape task. In contrast, the third and the fourth color (white and yellow) were presented as infrequent oddball-colors and appeared exclusively in the shape task. One of these colors had to be completely ignored (oddball 1), while the other one required subjects to reverse the initially prepared stimulus-response mapping and instead use a third response button (oddball 2; see also: below). Bivalent stimuli were presented in order to keep up subjects' attention and create an experimental situation in which subjects were engaged in goal-directed behavior on every trial. Further, subjects were

occasionally required to adjust their task goal to the unexpected occurrence of an infrequent deviant color in the shape task (oddball 2). As only one of the stimulus-dimensions was response-relevant within a single trial most of the target-stimuli could either be congruent (i.e., both the relevant and the irrelevant dimension were mapped to the same response button) or incongruent (i.e., the two stimulus-dimensions were mapped to different response buttons).

Since the major aim of the present study was to reveal neural responses associated with different types of behaviorally relevant salient events, that were attributable to either a reward association or to the active behavioral adjustment towards a low-frequency event which was however not associated with a reward (i.e., behavioral relevance through a manual response), I systematically varied the <u>behavioral relevance</u> and the <u>reward association</u> of experimental events by using a strictly factorial design:

In all, four different types of **"critical low-frequency (color) events"** were presented in the shape task, which occurred with an equally low frequency (~ 3,6% of all trials). These four critical events in the shape task were:

    A) Oddball 1.1: rare color white, *rewarded* and response irrelevant (40 trials)

    B) Oddball 1.2: rare color white, not rewarded and response irrelevant (40 trials)

    C) Oddball 2.1: rare color yellow, *rewarded* and <u>response relevant</u> (required a different button press) (40 trials)

    D) Oddball 2.2: rare color yellow, not rewarded and <u>response relevant</u> (required a different button press) (40 trials)

Deviant events were always presented in the currently irrelevant stimulus dimension color and had to be treated by the subjects as follows: While the two <u>response-relevant oddball events</u> (2.1 and 2.2) required subjects to ignore the shape dimension and switch from the already prepared shape task set to the color dimension and the oddball task set to execute the respective manual response (cf., Fig. 5, p. 43), the remaining two oddball events (1.1 and 1.2) had to be ignored. Instead, participants had to respond according to the respective shape of the object. Further, 50% of the oddball events (1.1 and 2.1) were associated with the chance to gain a reward for correct and fast performance. This was also the case for half of the remaining experimental trials, which were also associated with a <u>reward for correct performance</u>. Therefore, reward was no low-frequency event in itself (i.e., 50% of all trials were associated with the chance to gain a reward), but could occur in
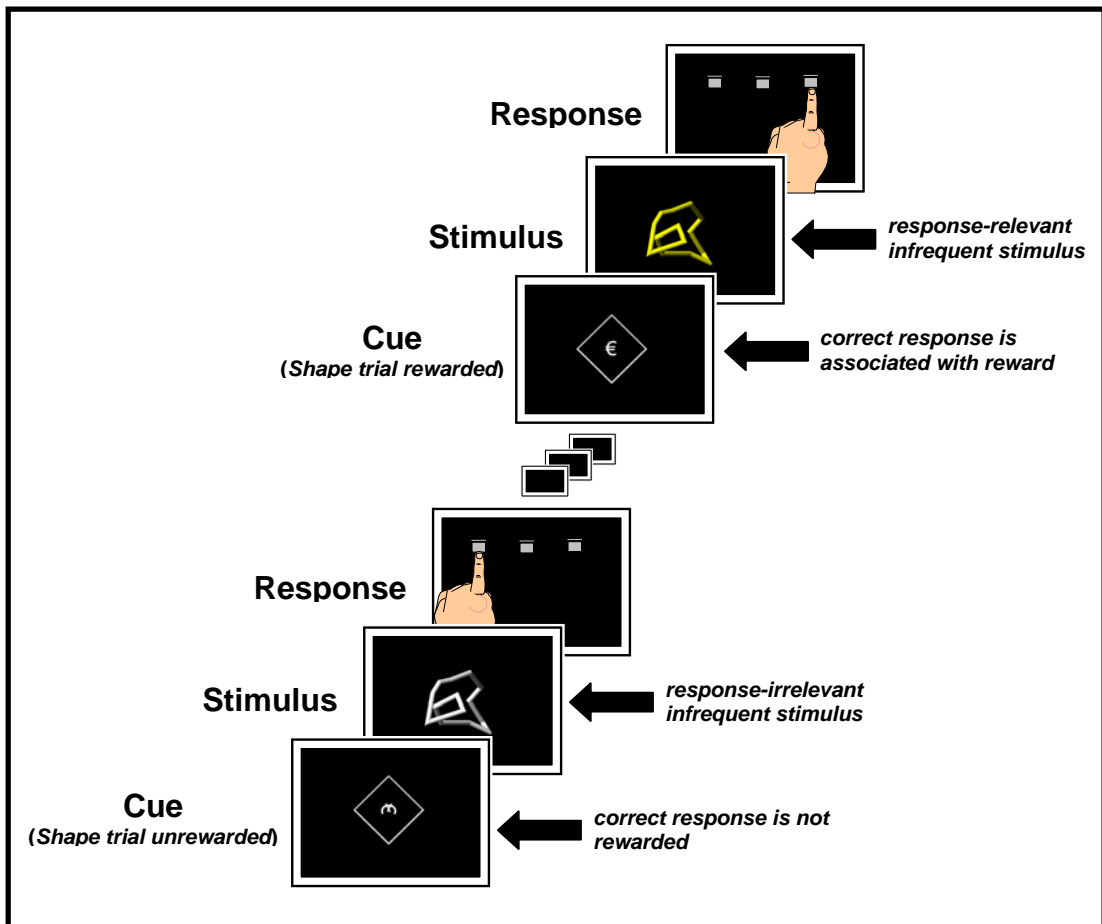
Figure 5: Example of experimental trial sequence.

association with one. With regard to rewarded trials, it was decided to refrain from giving subjects an immediate feedback directly after response execution, as previous studies had already revealed that subjects had been usually able to appraise their own performance quite accurately (i.e., whether they committed an error or not). Instead, reward was determined by a ranking-list of all participants, which was based on the overall mean performance (i.e., mean reaction times and error rates) of individual subjects in rewarded trials. Accordingly, the top three players with respect to their performance in trials with a reward association won an additional award of € 50 each. This competitive setting was intended to create both the incentive for optimization of performance in reward-trials and to keep up a constant arousal or salience level with regard to the individual rewarded trials throughout the whole experiment. Further, inclusion of all rewarded trials in a ranking-list was sought to prevent subjects from counting the individual trials associated with a reward.
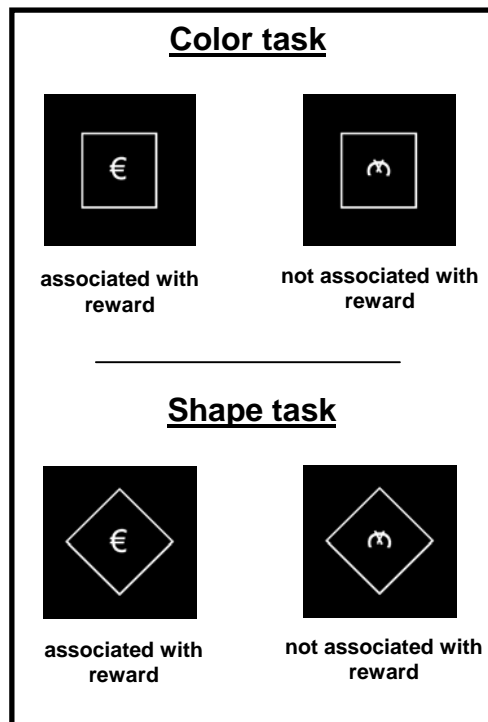
Figure 6: Cues of color and shape task.

In addition to the critical low-frequency events, we also prespecified 80 **"critical congruent shape trials"** half of which were also associated with reward for correct performance. They were introduced to create a baseline condition for the subsequent subtraction contrasts assessing oddball effects, because congruent trials were not assumed to trigger an orienting reflex since they were neither infrequent nor were they expected to elicit a behavioral conflict as the response assigned to both the relevant and the irrelevant stimulus dimension had to be executed with the same response button. Additionally, "critical congruent trials" also allowed the detection of the neural correlates of reward processing *per se* (i.e., reward associated with an event of normal frequency that elicited no orienting reaction). However, from subjects' perspective these congruent shape trials did not differ from the remaining congruent trials that occurred in the shape task. Further, these prespecified congruent events – like the infrequent oddball events – were balanced with respect to their preceding trials and were always cued as repeat trials (i.e., were always preceded by a shape trial, which was congruent). For that reason, significant differences in the BOLD response that were observed in the direct comparison between different "critical events", like for example in the comparison between relevant oddballs and critical congruent trials (cf., Table 2, p. 61), were not a result of the variation in preceding trials, but could exclusively be ascribed to the conditions themselves. In addition, "critical congruent events" were positioned at least 2 trials apart from oddball events, which further allowed for a quite similar modulation of the BOLD response for all above described "critical events of interest".

Since a minor purpose of the current study was the replication of the results from a previous study (Gruber et al., 2006, in prep.), the experimental trial structure was created as similar as possible to that of the prior study. Accordingly, each trial had a

duration of 1.75 s. At its beginning participants were instructed by a cue to either respond to the color or the shape of abstract geometric target-objects. Additionally, cues also informed participants about whether a trial was associated with the chance to gain a reward contingent on performance or not. The task cue consisted of a white frame (either a square-shaped frame for color or a diamond-shaped frame for shape; both with equal side length as the diamond was simply a square rotated by 90°) which surrounded either an Euro-symbol in its center (in trials with reward association) or an abstract symbol, which consisted of the dissembled parts of the Euro symbol (in trials that were not associated with a reward; cf., Fig. 6, p. 44). The similarity of the visual cues – especially with respect to their visual complexity – was deliberately chosen to avoid disparity in brain activation attributable to striking differences in visual stimulation. Nevertheless, the cues still allowed a clear distinction between the two tasks and the respective trial-reward association. The task cue was presented for 500 ms on a black screen and was chosen pseudo-randomly for each trial. Thus, the upcoming task was unpredictable for the subject, as was the occurrence of an infrequent deviant. Cue-offset was followed by a blank-screen-delay (i.e., a black default screen) for 250 ms before the target stimulus appeared. Target stimuli were presented for a total duration of 750 ms and were followed by another blank-screen-delay for 250 ms before the next trial began. The response phase – starting with target-onset – lasted 1000 ms until the trial ended. Responses made outside of this time-window were recorded as response omissions.

The beginning of each trial was synchronized with a new MRI scan. Altogether, the experiment consisted of 1120 trials. In addition to the above-described 240 "critical events of interest" the remaining trials consisted of 400 congruent and 160 incongruent trials in the shape task and 240 congruent and 80 incongruent trials in the color task, which were counterbalanced and pseudorandomly interspersed between the "critical events". Color trials were included in the experiment with the intent to keep up subjects' constant attention as they were occasionally required to switch to another stimulus dimension or had to respond to incongruent trials. However the major focus of this thesis was on the prespecified "critical events" and for that reason we won't report any other activations but only those associated with the "critical events of interest".
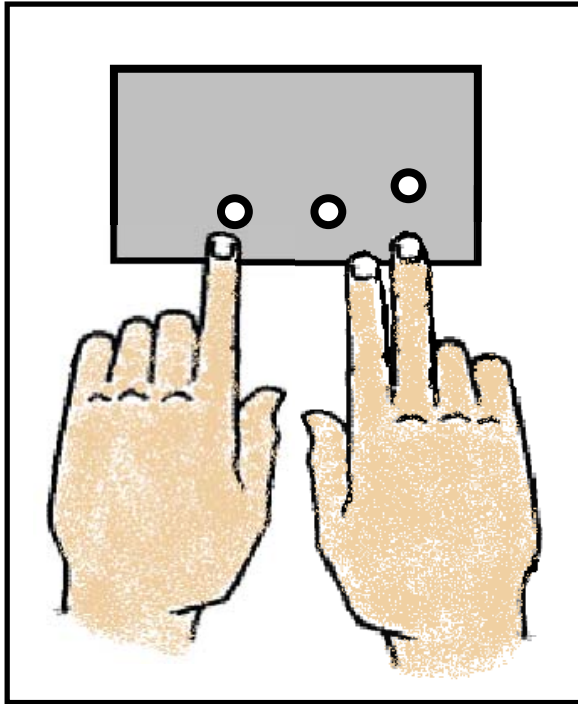
Figure 7: Button box and the respective fingers used for execution of the manual response.

In order to avoid any neural effects that might have been associated with a differential saliency of the oddball-colors white and yellow (i.e., stimulus-specific effects), in half of the participants the color mapping described on page 31 was reversed (i.e., irrelevant oddballs 1.1 and 1.2 were presented in yellow, while behaviorally relevant oddballs 2.1 and 2.2 appeared in white). Subjects were randomly assigned to one of these mappings. Moreover, different from the previous study by Gruber et al. (2006, in prep.) participants used both their left and right hand to respond to the target stimuli (cf., Fig. 7, this page). Accordingly, in half the participants the response to the behaviorally relevant oddballs had to be executed with the index finger of the left hand while the standard responses (i.e., left manual response to the color blue or the first object, right manual response to the color red or the second object) had to be executed with the index and the middle finger of the right hand. The remaining half of the participants responded to the relevant oddballs with the middle finger of the right hand while the index finger of the left hand and the right index finger were used for the frequent standard responses. This systematic variation of manual response mapping was employed because we wanted to avoid any strongly lateralized motor activations being associated with the additional button press with respect to one of the response-relevant low-frequency events. Still, it was not feasible to also use the third possible variation (i.e., left manual response with left index finger, right response with right middle finger and additional button press as response to infrequent deviant with right index finger) as this mapping probably would have been counterintuitive and might have led to an overall increase in reaction times and/ or error rates, which would have been unfair for the respective participants regarding their opportunity to win the additional €50.

Figure 8: Siemens MRT Allegra Scanner in BIC (Frankfurt/Main)
(Fig. 8 was taken from the official BIC-website: http://www.bic.uni-frankfurt.de/).

The neuropsychological experiment was programmed with the Presentation software (Version 9.20; Neurobehavioral Systems, Inc.; Albany, U S A) that controlled time of stimulus presentations and recordings of reaction times, error and omission rates both during initial training and in the scanner. As it was important for subjects to perform as accurate and fast as possible, subjects were trained in the week before the experiment on a PC outside the scanner for at least 567 trials and also got the chance to become familiar with the response-box in the scanner. The training also pursued the purpose to eliminate any novelty effects that might have been elicited by the infrequent oddball colors.

7. Acquisition of the fMRI-data

The experiment was carried out in a 3-Tesla MRI scanner (Siemens MRT Allegra; Siemens, Germany; see Fig. 8, this page) In an initial session, a high-resolution structural scan (3-D MPRAGE) was obtained for each subject. Thirty axial slices (voxel size 3 x 3 x 3 mm^3, distance factor = 0.1) parallel to the AC-PC plane were acquired in ascending direction after having obtained the structural T1-weighted 3-D MPRAGE data set as the anatomic reference scan. The gradient EPI sequence (TR 1.75 s, TE 30 ms, flip angle 60°, field of view 195 mm, 65 x 65 matrix) acquired a total of 1164 image volumes. Each run began with a fixation period including 8

"dummy" volumes, which were subsequently discarded to also allow for T1 equilibration effects.

As already described above, stimulus presentations and recordings of reaction times, error and omission rates were performed with the Presentation software. Stimuli were back projected on a translucent screen, which participants viewed through a mirror during the fMRI acquisition. The head was stabilized by small cushions to avoid head movements during scanning. Triggering of the visual stimulation by the scanner impulse during the functional data acquisition was also conducted through the Presentation software.

8. Data analyses

In order to test for significant effects of experimental conditions both the behavioral performance and the fMRI BOLD response were statistically analyzed.

8.1 Analyses of the behavioral data

Statistical analysis of the behavioral data was done using the software-package SPSS for Windows (Version 13.0) by SPSS Inc. (2004).

After assessing the descriptive statistics, the distribution of the behavioral data was assessed for a significant deviation from a gaussian normal distribution. For this purpose, the Kolmogorov-Smirnov-Test was used assuming a significant deviation from the normal distribution at $P < 0.05$ (cf., Lamprecht, 1999). As this test did not reach statistical significance, the application of parametric tests was justified. In a second step, the dependent variables reaction time and percent rate of correct responses were examined with a two-way analysis of variance [Abbr. ANOVA] with the two independent predictors reward association and experimental condition treating subjects as a random effect. Error and omission trials were thereby excluded from the reaction time analysis. The ANOVA is a parametric analysis that tests for significant differences between the means of two or more groups. With more than one independent predictor the factorial ANOVA also tests for interactions between the predictors (cf., Köhler et al., 1996; Backhaus et al., 2000). However, even though an ANOVA provides information on whether there is a significant difference

between conditions, it does not show which conditions were significantly different from each other. For this reason, performance differences between individual conditions were assessed with a *post-hoc* t-test which was corrected for multiple comparisons using the Bonferroni-correction. P-values are reported for a two-tailed t-test without a directed hypothesis. Further, the effects of the respective oddball color and the finger mappings on behavioral performance were also assessed in an ANOVA with the two independent predictors oddball color and finger mapping.

8.2 Analyses of the fMRI data - Data preprocessing and statistical methods

The neuroimaging data were both preprocessed and analyzed using statistical parametric mapping 2 [Abbr. SPM2] from the Wellcome Department of Cognitive Neurology (London, UK), which is a voxel-based approach that permits the inference on regionally specific responses to experimental factors (cf., Friston, 2003).

After an initial preparation of the functional images for preprocessing with SPM2, the following steps were consecutively applied:

1. a coregistration of anatomical and functional images
2. image realignment and unwarping of functional images to the first functional echo-planar image [Abbr. EPI] in order to reduce movement-related effects
3. a correction for slicetime acquisition differences
4. a normalization into standard stereotactic space (to the skull-stripped EPI template provided by the Montreal Neurological Institute [Abbr. MNI]) and
5. spatial smoothing of the functional images with an isotropic Gaussian kernel filter of 12 mm full-width half-maximum [Abbr. FWHM] in order to facilitate inter-subject averaging.

8.2.1 Preparation of the images for preprocessing

After initial reorientation of the anatomical T1-image of each subject, which prepared the T1 for its further use in SPM2, all images (i.e., both the T1 and all EPIs) were flipped from the radiological to the neurological image orientation. The first 8 volumes from each scan were then discarded as these volumes only contained the

fixation period and T1 equilibration effects which were of no interest for the further analyses. The next consecutive step consisted of positioning the origin of the coordinate system in the lowermost point on the cutting edge of the anterior commisure (in the median-sagittal plane) as a reference point in both the T1 and the first EPI of each subject, respectively. Positioning of the origin as a reference point was needed for the subsequent coregistration of the T1-image on the first EPI (see below). The remaining EPIs were also reoriented according to the orientation of the first EPI.

8.2.2 Image preprocessing with SPM2

Spatial preprocessing usually comprises the following steps: coregistration, realignment, correction of slicetime acquisition differences, normalization and smoothing. The initial **coregistration** of the T1-anatomical images on the first EPI was done to improve the subsequent normalization of the images to standard stereotactic space. It was then followed by **image realignment** aiming to reduce unwanted variance components induced by a subject's movement during the whole scanning, because changes in signal intensity over time can arise from head motion confounding with experimentally induced activations (cf., Friston, 2003). Image realignment for individual subjects was done on a reference scan (in this study the first scan of the whole experiment) on which all other scans were realigned. During realignment SPM2 created a mean image based on the functional images of each participant. This image was needed for the later normalization procedure (see below). Further correction for local distortion effects was also applied using the "realign and unwrap" function.

The next procedure corrected for **slice-time acquisition differences**. In fMRI-studies a whole brain volume consists of multiple slices (e.g., 30 slices in the current study), which were acquired at slightly different time points. For that reason, temporal realignment was used in order to ensure that the data from any given volume were sampled at the same time (cf., Friston, 2003). In the current study, the 15th slice was taken as reference slice on which the temporal interpolation was based.

To be able to assign an observed response to a particular brain structure, especially when data from different subjects are compared, it is necessary that the data conform

to an anatomical frame of reference (cf., Friston, 2003). Accordingly, the time-series of images has to become realigned and mapped into some standard anatomical space (e.g., the stereotactic space of Talairach and Tournoux). With regard to the current study, all functional images from each subject were **normalized** to a voxel size of 3x3x3 mm on the skull-stripped SPM2 EPI-template into the standard reference-space in SPM2 provided by the Montreal Neurological Institute using the mean image of each subjects as source image. This allowed me to remove inter-individual differences and enabled the subsequent analysis of the data from a group of individuals.

Finally, the functional MRI data were **spatially smoothed** before they entered statistical analysis. The current study used a high smoothing factor (FWHM = 12 mm) in order to be able to express substantial homologies in functional anatomy derived from inter-subject averaging (for a detailed description please see: Friston, 2003).

8.2.3 Statistical analyses of the fMRI data with SPM2

For statistical analysis of the fMRI-data a general linear model [Abbr. GLM] in combination with Gaussian Random Fields [Abbr. GRF] used to resolve the multiple comparison problem, was applied to the time course of activation of each voxel. A vector representing the temporal onset of stimulus presentation (for each stimulus type) was then convolved with a canonical hemodynamic response function, in order to produce a predicted hemodynamic response to each experimental condition. Linear t-contrasts were defined for assessing the specific effects of each "critical condition of interest". The specific statistical t-contrasts that were calculated are described in detail in the results section. SPM creates statistics by doing a separate statistical analysis for each voxel in the brain volume (for a more elaborate outline on the GLM and GRF used in SPM2 please see the related chapters in Frackowiak et al., 2003). **T-contrasts in SPM** test against the nullhypothesis that there is no linear relationship between an experimental variable and the voxel data, and that beta, the slope of the line, will not be significantly different from zero. The t statistic is the least squares estimate of the slope, divided by a measure of the error of the slope, and is therefore an index of how far the slope differs from zero, considering the given

error. Knowing the distribution of the t statistic, one can say that, for instance, with 10 degrees of freedom, by chance a t statistic of 7.96 or greater occurs 0.0006 percent of the time, if the nullhypothesis is true (i.e., the p value is 0.000006; see: http://www.mrc-cbu.cam.ac.uk/Imaging/Common/spmstats. shtml).

In the **first level event-related analysis** 18 event types were defined (6 "critical events of interest" and the 12 remaining events also including the 4 cue-events). Event types were time-locked to condition onset (cue onset and target onset, respectively). The resulting design matrix was used to test for brain activity changes associated with the "critical events of interest" which occurred at different time points in the course of the experiment.

Group effects were assessed by a **second level random-effects analysis** based on single subject contrast images. Due to *a priori* hypothesis concerning the orbitofrontal cortex, which has been already shown to be involved in the processing of both infrequent events and rewarded events, the summary statistical parametric maps were thresholded at P < 0.005, uncorrected for multiple comparisons (Friston, 1997), with a voxel extent greater than 10 voxels, if not otherwise reported. Based on the previous study (Gruber et al., 2006, in prep.), activations in the "adaptive processing network" (e.g., in the temporoparietal junction, anterior insular cortices and anterior cingulate; Kiehl et al., 2005a) were further predicted to occur in subtraction contrasts testing for neural responses elicited by behaviorally relevant oddballs. However, for the remaining regions the threshold, P < 0.005, uncorrected, does not provide adequate protection against type I errors in the whole brain. For that reason, these activations were mainly reported for completeness and required a careful discussion.

Also for the purpose of the direct **examination of the first working hypothesis**, which concerned the replication of the results of the previous study (Gruber et al., 2006, in prep.) an additional statistical procedure was applied. By using an **inclusive masking procedure** with the WFU-Pickatlas toolbox from the Wake Forest University School of Medicine (Maldjian et al., 2003) the statistical analysis was only restricted to comparisons being made within a subset of the brain volume (i.e., restricted to voxels within the mask). In order to create the mask, a contrast from the previous study (Gruber et al., 2006, in prep.) was used which had removed the confounding effect of behavioral relevance *per se*. Even though the currently applied one-session design had certain advantages over a multiple-session design from the

previous study (Gruber et al., 2006, in prep.), the one-session design also suffered from the decisive disadvantage that it did not allow for a clear distinction of neural activations that were exclusively attributable to the behavioral relevance *per se* including the change in task set (i.e., the oddball-color indicated a change from the shape task set to the oddball color task set) and the prepared stimulus-response association, which was independent from the effect of infrequency, and those that were exclusively attributable to the fact that an event was both infrequent and behaviourally relevant. The previous study had solved this problem by presenting the behaviorally relevant oddball color frequently in the shape task of the third session. This had allowed Gruber et al. (2006, in prep.) to calculate a contrast, which combined the direct subtraction contrasts of:

1. [behaviorally relevant infrequent events (session 2) - irrelevant infrequent events (session 1)] versus

2. [behaviorally relevant infrequent events (session 2) - behaviorally relevant frequent events (session 3)].

In that way Gruber et al. (2006, in prep.) had been able to measure out both the mere effect of infrequency attributable to both the low-frequency events presented in sessions 1 and 2 and the effect of the behavioral relevance of events that required a rapid behavioral adjustment, which occurred either infrequently in session 2 or frequently in session 3. This allowed the interpretation that the remaining activations indeed represented the **pure interaction of behavioral relevance and infrequency**, which exclusively occurred in session 2 of their study. That means, that masking the respective subtraction contrast from the current study (i.e., the contrast [behaviorally relevant oddballs - irrelevant oddballs]) with that previous contrast, also allowed me to infer that the presently observed activations were probably associated with the mere interaction of infrequency and behavioral relevance.

Finally, the **anatomic localization of the activations** detected in the group analysis was done by both making use of the aal-software by Tzourio-Mazoyer et al. (2002), that allowed for an approximate automated anatomical labeling in SPM2, and the anatomical atlas of the human brain by Duvernoy et al. (1999) with photographs of the three-dimensional sectional anatomy of the *post-mortem* brains and MRI-based pictures presented in the three sectional orientations (coronal, axial and sagittal). The combination of both methods allowed a quite fine-grained anatomical labeling of the detected local maxima.

V. Results

1. Behavioral results

Mean reaction times [Abbr. RTs] and percentages of correct responses [Abbr. CRs] were compared across different events of interest. Reward did not exhibit a significant effect on overall performance (F_{CRs} = 1.92, P = 0.199; F_{RTs} = 0.001, P = 0.973; cf., Figs. 9 & 10, p. 55) and the interaction between reward and experimental condition also did not reach statistical significance (F_{CRs} = 1.57, P = 0.174; F_{RTs} = 1.53, P = 0.187). Nevertheless, performance was significantly affected by experimental condition (F_{CRs} = 8.61, P = 0.0001; F_{RTs} = 44.17, P = 0.0001). Bonferroni-corrected *post-hoc* t-tests revealed individual condition effects. RTs were significantly increased when subjects responded to behaviorally relevant infrequent events when compared to both irrelevant oddballs (P = 0.0001) and critical congruent events in the shape task (P = 0.0001; cf., Fig 9, p. 55). In addition, subjects committed significantly more errors when they responded to response-relevant oddballs compared with a critical congruent shape stimuli (P = 0.0001; see also: Fig. 10, p. 55) and there was also a trend for an increase in error rates when compared to those trials including an irrelevant oddball (P = 0.094). However, ignoring the infrequent deviant in the shape task and reorienting attention to the shape dimension neither led to a significant increase in RTs (P = 0.669) nor in the rate of errors committed (P = 1.0) when compared to performance in critical congruent shape trials, even though subjects on average responded faster to critical congruent shape trials (cf., Fig 9, p. 55) and made less errors when processing critical congruent shape trials in comparison with irrelevant oddball trials (cf., Fig. 10, p.55).

In addition, there was a slight increase in overall RTs when the response-relevant oddballs were white and the irrelevant infrequent stimuli were yellow (mean RTs $_{\text{mapping I}}$ = 648.89 ms, SD = 48.70 ms) compared to the other mapping (mean RTs $_{\text{mapping II}}$ = 629.82 ms, SD = 84.44 ms), which however did not reach statistical significance (F = 2.40, P = 0.124). With regard to the rates of correct responses, oddball-color mapping exhibited a significant effect on performance which lead to a decrease in overall error rates when the relevant oddball was white (mean $CRs_{\text{mapping I}}$ = 91.25%, SD = 9.23%; mean CRs $_{\text{mapping II}}$ = 94.70%, SD = 7.69%; F = 5.91, P = 0.016). These findings indicated an overall speed accuracy trade-off. That means that
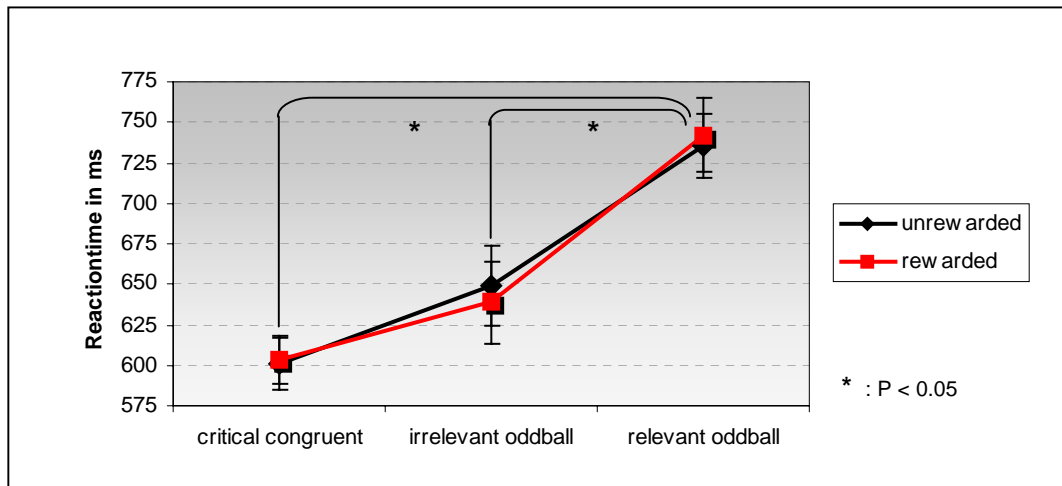
Figure 9: Oddball effect and effect of reward in the shape task I. Mean RTs and standard errors (n=10).
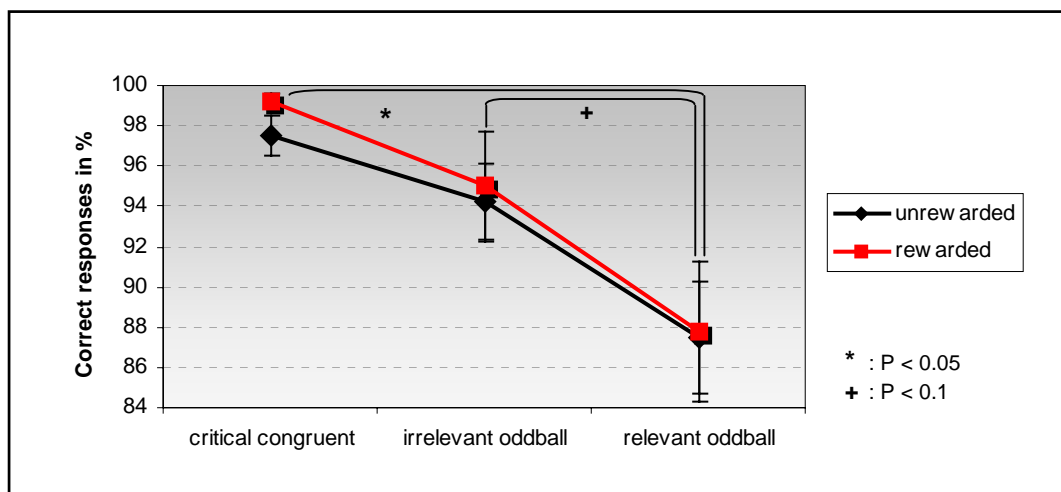
Figure 10: Oddball effect and effect of reward in the shape task II. Mean percentage-rates of correct responses and standard errors (n=10).

subjects with mapping 1 performed more slowly but also more accurately, while subjects with the second mapping responded faster by committing significantly more errors. In contrast, the two finger mappings (i.e., whether subjects responded with the left index finger or the right middle finger to the response-relevant infrequent stimulus) did not significantly influence behavioral performance (F_{RTs} =1.31, P = 0.255; F_{CRs} = 0.838, P = 0.361). Finally, the interaction between finger and color mapping also significantly affected performance, which was probably attributable to the effect of color mapping (F_{CRs} = 14.644, P = 0.0001; F_{RTs} = 5.01, P = 0.027).

With respect to the competition in the task-switching experiment, three male participants showed the best overall performance according to the ranking position of both their mean RTs and CRs and therefore won the additional award of €50 each.
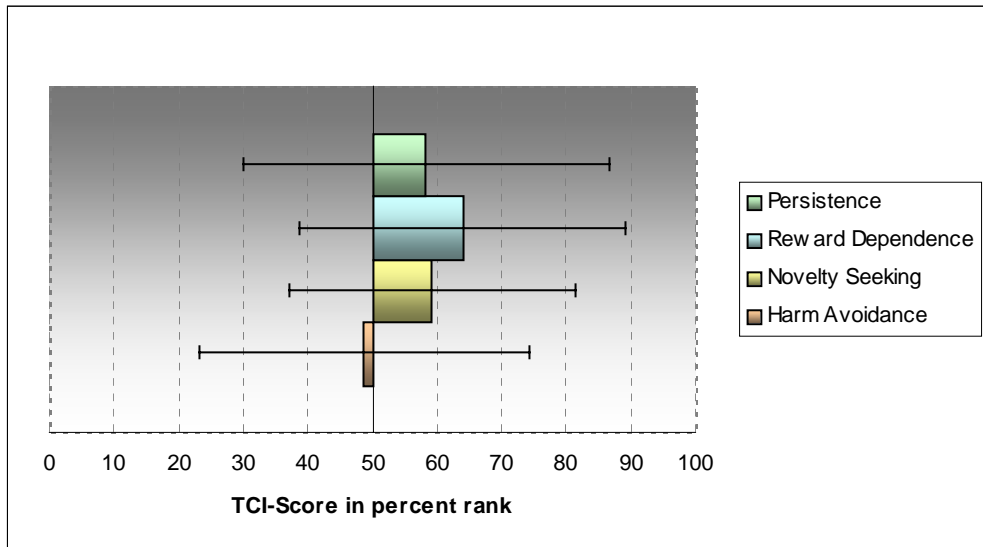
Figure 11: Temperament dimensions of the TCI (Cloninger et al., 1993). Mean scores and standard deviations of all participants (n=10).
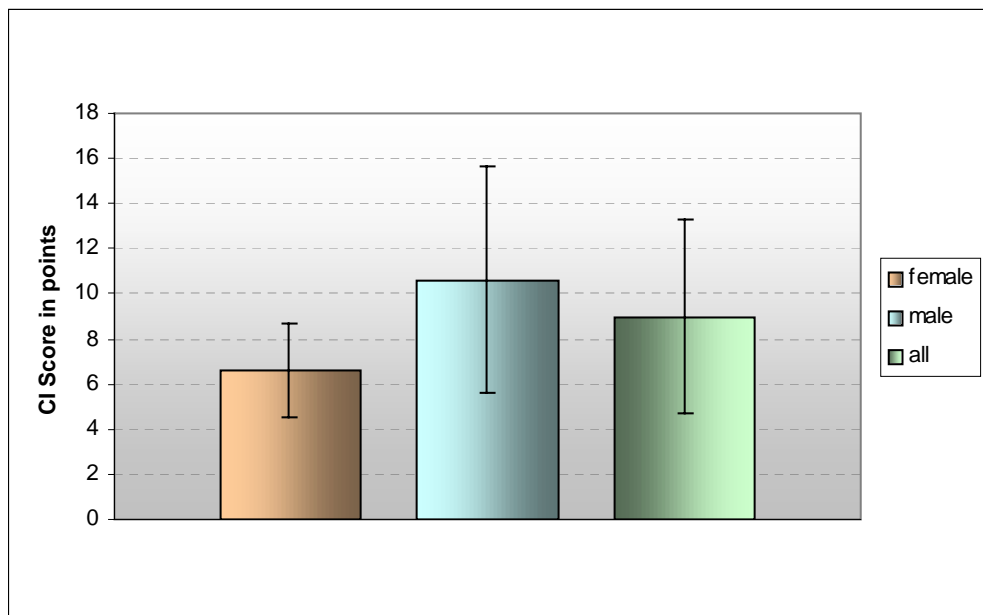
Figure 12: Gender differences in competitiveness. Mean scores and standard deviations of the competitiveness-index (Houston et al. 1992) of all female subjects (n=5), all male subjects (n=5) and all participants (n=10).

2. Personality profiles

The TCI- and CI-scores showed a considerable variation across subjects (cf., Figs. 11 & 12, this page). However, the overall mean scores of the TCI-temperament dimensions lay within the normal range (cf., Richter et al., 1999).

With regard to the CI, two females and one male subject showed a sub-average score, while one male participant showed higher than average competitiveness, when

categorizing individual CI-scores with respect to the respective norm-population (see also: Material and Methods, p. 41). The remaining participants exhibited CI-scores that lay within the normal range with males on average scoring higher than females, even though this difference did not reach statistical significance (cf., Fig. 12, p.56).

3. FMRI results

The analyses of the imaging data pursued two goals. While the minor goal was a replication of the results from the previous study by Gruber et al. (2006, in prep.), the major goal was the comparison of different forms of biologically significant events (i.e., events with a reward association and oddball events that required a behavioral adjustment), with a particular focus on the associated orbitofrontal activations.

For replication purposes, firstly the separate contrasts for neural responses associated with either response-irrelevant oddball events or behaviorally relevant oddballs requiring a behavioral adjustment were calculated. Then different oddball events were directly compared in order to reveal activations that were attributable to the effect of behavioral relevance of infrequent events without being confounded by the effect of infrequency *per se*. This comparison of behaviorally relevant oddballs with irrelevant ones was further inclusively masked with a contrast from the prior study by Gruber et al. (2006, in prep.), which allowed me to reveal activations that were found to be exclusively associated with the interaction of infrequency and behavioral relevance in the previous study, however, without being confounded by either effects of infrequency or behavioral relevance *per se* (see also: Material and Methods, pp. 52).

In a second step, the separate contrasts for the reward events of interest were calculated. These contrasts were sought to reveal activations that occurred in association with either reward of critical congruent stimuli presented in the shape task or reward of irrelevant oddball events.

Finally, direct subtraction-contrasts between events with a reward association (either critical congruent trials with a reward association or irrelevant oddballs that were associated with reward for correct performance) and behaviorally relevant oddballs were calculated. These latter contrasts were intended to reveal significant differences between neural responses associated with reward processing and those elicited by

infrequent events that required a behavioral adaptation, but were however not associated with a reward.

3.1 Effects of infrequent deviance and behavioral relevance of infrequency

In order to reveal those brain regions which were activated by either the presentation of infrequent irrelevant deviants or by an infrequent event that was behaviorally relevant (in this case the response-relevant oddball, that was not associated with the chance to gain a reward) activations for the following three comparisons are reported:

1.) [all trials with an irrelevant oddball stimulus without reward association – congruent shape trials[1] without reward association],

2.) [all trials with a behaviorally relevant oddball without reward association – congruent shape trials without reward association] and

3.) [all trials with a behaviorally relevant oddball without reward association – all trials with an irrelevant oddball without reward association].

While the first subtraction-contrast was intended to reveal activations associated with the sheer infrequency of an event that was irrelevant for the behavioral response to be given (cf., Table 1, p. 59), the second one aimed at revealing neural activations that were attributable to both the rareness of the event and its behavioral relevance (i.e., the requirement for a behavioral adjustment) as well as the interaction between these two stimulus-attributes (cf., Table 2, pp. 61). Finally, the third subtraction contrast was sought to uncover activations that may be ascribed to the interaction of behavioral relevance and rareness (cf., Table 3, pp. 64), but not to the effect of infrequency *per se*.

3.1.1 Response-irrelevant infrequent stimuli vs. congruent shape stimuli

Activations associated with the effect of infrequency *per se* are listed in Table 1 (p. 59) and are further displayed on Figure 13A (p. 63). Irrelevant infrequent deviance

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[1] In the remaining sections I will always refer to the prespecified **"critical congruent shape trials"** (cf., Material & Methods, p. 44) as **"congruent shape trials"** or **"shape congruency"**, if not indicated otherwise.

Table 1: Neural activations evoked by irrelevant oddballs

Irrelevant oddballs without reward association vs. congruent shape trials

Region	MNI coordinates	Statistical effects (T-value)
Frontal lobes		
R superior frontal cortex	18 15 57	3.63
L middle frontal gyrus/ inferior frontal sulcus	-54 24 33	3.91
R middle frontal gyrus	39 39 36	4.87
R anterior orbital gyrus	36 57 -15	2.12[1, 2]
R anterior medial orbital gyrus	21 48 -18	2.06[1, 2]
R posterior orbital gyrus	18 21 –21	2.69[1]
R pre-supplementary motor area/ supplementary motor area	3 18 60	4.12
Parietal lobes		
L intraparietal cortex	-33 –72 51	2.72[1]
R intraparietal cortex	36 -60 39	3.90
Occipital lobes		
L middle occipital cortex	-30 -93 3	5.38
R middle occipital cortex	30 -90 12	5.90
R fusiform gyrus/ inferior occipital cortex	36 -63 -12	6.07
Cerebellum		
R cerebellum	24 -33 -27	3.62

If not indicated otherwise activations were thresholded at P<0.005, uncorrected; clustersize > 10 voxels
[1]Activation was thresholded at P<0.05, uncorrected
[2]Clustersize < 10 voxels

was associated with a significant activation in bilateral middle frontal gyri, right superior frontal cortex and in the right pre-supplementary motor area [Abbr. pre-SMA] partly extending into the SMA proper. In addition, activations in both right and left intraparietal cortex were also observed, whereby the latter activation only came up, when the statistical criterion was lowered to P < 0.05, uncorrected. Finally, irrelevant oddballs also led to activations in bilateral extrastriate, right secondary visual cortex and in the right cerebellum.

At the statistical threshold of P < 0.005, uncorrected, infrequency *per se* did not activate the orbitofrontal cortex as it was already expected from the results of the

previous study by Gruber et al. (2006, in prep.). Nevertheless, when lowering the statistical threshold to P < 0.05, uncorrected, distinct orbitofrontal activations within right posterior orbital gyrus, in the right anterior orbital gyrus and adjacent right anterior medial orbital gyrus were detected. Interestingly, these clusters strongly overlapped with the some of the orbitofrontal activations observed in the following comparison between behaviorally relevant oddball events and congruent shape trials (cf., Table 2, p. 61).

3.1.2   Behaviorally relevant infrequent stimuli vs. congruent shape stimuli

Activations associated with the effect of behaviorally relevant infrequent deviance are listed in Table 2 (pp. 61) and are further displayed on Figure 13B (p. 63). Behaviorally relevant oddballs led to significant bilateral activations in the posterior orbital gyri and adjacent parts of the cortex along the H-shaped sulci, in the right anterior orbitofrontal cortex as well as in left frontoopercular cortex and adjacent parts of the posterior orbitofrontal cortex. Further, in the frontal lobe significant activations were detected in the middle frontal gyrus on both sides and in the superior frontal sulcus on the left. There was also a local maximum in the left pre-SMA further extending into the SMA and a smaller cluster in the cingulate gyrus just above the corpus callosum. Behaviorally relevant oddballs activated somatosensory cortices in both hemispheres partly extending into parietal cortex. In addition, significant activations were also found bilaterally in the intraparietal cortices as well as in the right angular gyrus extending into supramarginal gyrus with a maximum in the parietal subdivision of the TPJ, and the left precuneus exhibited two activation maxima. In the temporal cortex a significant activation within the left TPJ was further detected. Moreover, left middle and inferior temporal cortices also exhibited significant activation clusters. In the right hemisphere significant activations were detected in the inferior temporal cortex. Visual processing areas of the occipital cortex on the left and on the right, the latter also extending into gyrus fusiformis, were also activated by behaviorally relevant oddballs. Finally, the thalamus, the right amygdala and adjacent gyrus ambiens and the right cerebellum also exhibited significant activations.

Table 2: Neural activations evoked by behaviorally relevant oddballs

Relevant oddball without reward association vs. congruent shape trials		
Region	MNI coordinates	Statistical effects (T-value)
Frontal lobes		
L superior frontal sulcus/ middle frontal gyrus	30 0 51	4.25
L middle frontal gyrus	-54 18 39	4.95
R middle frontal gyrus/ inferior frontal sulcus	54 24 36	6.72
R anterior orbital gyrus	39 57 -12	3.84
L posterior orbital gyrus/ H-shaped sulcus	-24 27 -21	4.33
R posterior orbital gyrus/ H-shaped sulcus	21 21 -21	5.07
L frontoopercular cortex/ lateral posterior orbitofrontal cortex	-33 18 3	3.44
L pre-supplementary motor area/ supplementary motor area	-3 18 60	7.33
R cingulate cortex	3 -15 30	3.81
Parietal lobes		
L postcentral cortex	-57 -33 54	4.87
L postcentral cortex	-63 -21 24	4.84
R postcentral cortex	66 -12 36	5.54
R angular gyrus/ supramarginal gyrus (TPJ)	48 -51 33	4.71
L intraparietal cortex	-33 -72 51	4.12
R intraparietal cortex	36 -72 48	3.75
L precuneus	-9 –60 60	3.49
L precuneus	-15 –81 54	3.68
Temporal lobes		
L posterior superior temporal gyrus (TPJ)	-51 –42 27	3.62[1]
L middle temporal gyrus/ superior temporal gyrus	-57 -60 6	3.63
L inferior temporal sulcus/ inferior temporal gyrus	-51 –36 –21	3.65
R inferior temporal sulcus/ inferior temporal gyrus	60 -42 -15	5.63

If not indicated otherwise activations were thresholded at P<0.005, uncorrected; clustersize > 10 voxels
[1]Clustersize < 10 voxels

Table 2: continued

Relevant oddball without reward association vs. congruent shape trials

Region	MNI coordinates	Statistical effects (T-value)
Occipital lobes		
L inferior occipital cortex	-9 -105 -3	3.78
R inferior occipital cortex	21 –69 3	3.72[1]
R inferior occipital cortex/ fusiform gyrus	36 -75 -12	5.84
Deep gray nuclei		
L thalamus	-9 -18 -3	3.59
R amygdala/ gyrus ambiens	33 9 -27	3.74
Cerebellum		
R cerebellum	39 –42 -33	5.67

If not indicated otherwise activations were thresholded at P<0.005, uncorrected; clustersize > 10 voxels
[1]Clustersize < 10 voxels

3.1.3   Behaviorally relevant infrequent stimuli vs. irrelevant infrequent stimuli

This contrast was intended to reveal those regions that were selectively responsive to the effect of behavioral relevance of infrequency without being confounded by the effect of infrequency *per se*. In accordance with this assumption less cortical regions were found to be activated than in the comparison reported before. Results are listed in Table 3 (pp. 64) and displayed on Figure 13C (p. 63).

In this comparison significant BOLD responses associated with behaviorally relevant infrequent stimuli in the shape task were detected in right posterior orbitofrontal cortex as well as in bilateral frontoopercular cortices and neighboring posterior orbitofrontal cortices. In addition, a local maximum within right anterior lateral OFC was also observed in this comparison (cf., Fig. 14A, p. 67). Further, significant activations were observed within the left insular cortex, in the postcentral cortex bilaterally and in the left precuneus. The local maxima observed in the left and right posterior superior temporal cortices were located within the TPJ. In the right hemisphere a significant activations were further observed in the angular gyrus and adjacent supramarginal gyrus, which was located the parietal part of the TPJ. In
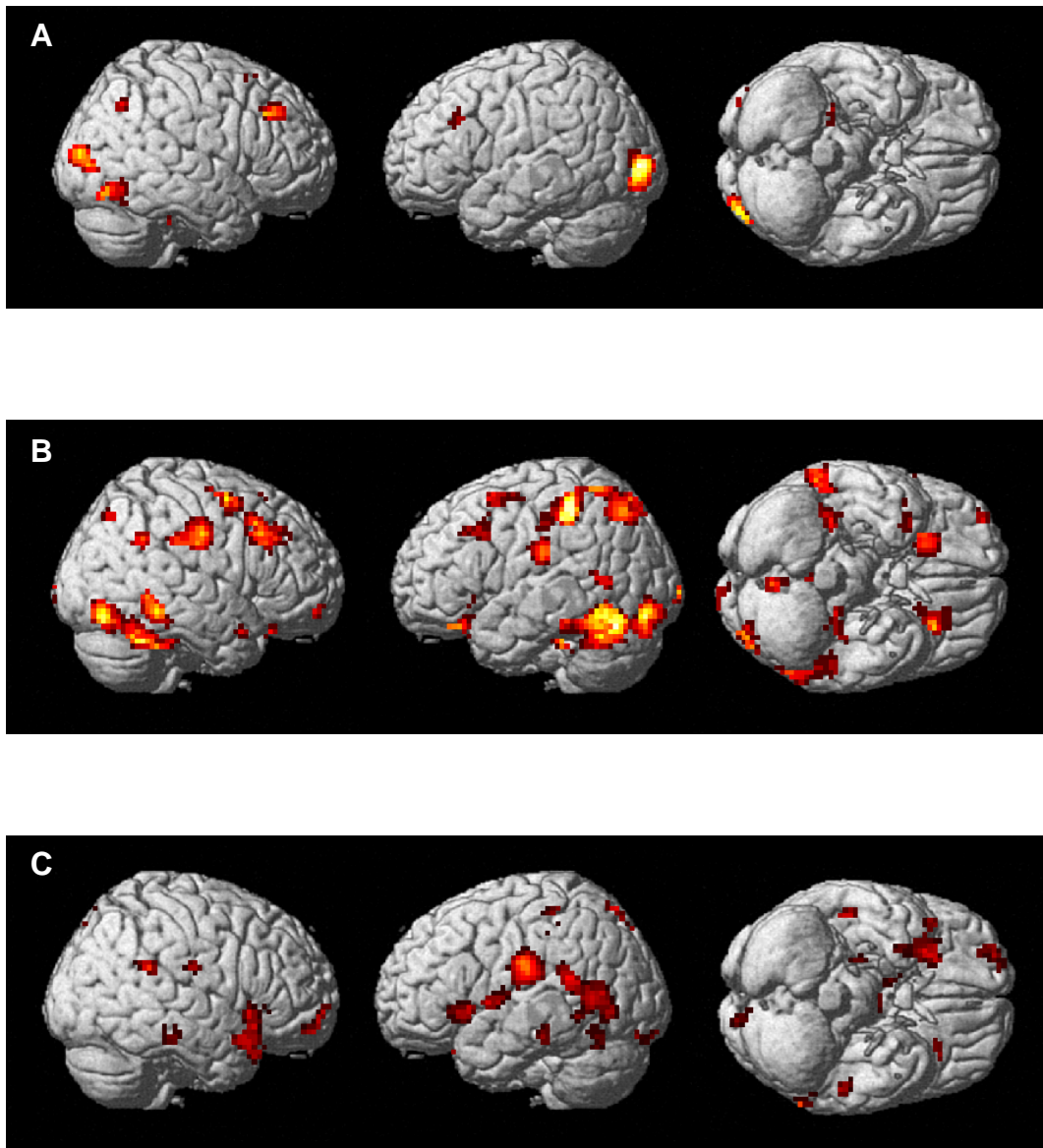
Figure 13: Oddball effects displayed on the rendered surface of the standard MNI-template at P< 0.005, uncorrected. (A) activations associated with irrelevant oddballs versus congruent shape trials; (B) activations associated with behaviorally relevant oddballs versus congruent shape trials; (C) activations associated with relevant oddballs versus irrelevant oddballs in the direct comparison of (B) minus (A).

addition, activations were found within left middle and inferior temporal cortices as well as right superior temporal gyrus. Visual processing areas of inferior occipital cortex and the cerebellar vermis were also activated by behavioral relevance of infrequency. Finally, significant activations were also detected in the thalamus, the left superior colliculus, the right amygdala. In addition, activation in the left amygdala was only detected, when lowering the statistical criterion to $P<0.05$, uncorrected.

In order to examine the first working hypothesis concerning the replication of the results of the previous study from my laboratory, I also assessed whether the currently observed activations, and in particular those in the OFC, were similar to

Table 3: Neural activations evoked by different forms of behavioral relevance

Regions	Behaviorally relevant oddballs vs. irrelevant oddballs		Irrelevant oddballs with reward association vs. irrelevant oddballs		Congruent shape trials with reward association vs. congruent shape trials*	
	MNI coordinates	Statistical effects (T-value)	MNI coordinates	Statistical effects (T-value)	MNI coordinates	Statistical effects (T-value)
Frontal lobes						
R anterior orbital gyrus	30 54 -15	4.67	-	-	-	-
L medial orbital gyrus	-	-	-15 36 –18	3.58 [1]	-18 39 –18	5.54
R posterior olfactory sulcus/ posterior medial orbital gyrus	-	-	18 24 -12	3.45	18 21 -15	3.54
R posterior orbital gyrus/ gyrus ambiens	27 18 -27	6.07 [2]	-	-	-	-
L frontoopercular cortex/ lateral posterior orbitofrontal cortex	-36 18 -3	5.23 [2]	-	-	-	-
R frontoopercular cortex/ lateral posterior orbitofrontal cortex	30 21 –9	4.04 [2]	-	-	-	-
L insular cortex	-48 0 3	4.07	-	-	-	-
Parietal lobes						
L postcentral cortex	-54 -33 57	3.60	-48 –27 60	4.60	-	-
L postcentral cortex	-66 -18 27	14.75 [2]	-60 –3 15	4.30	-	-
R postcentral cortex	66 -15 24	3.59	69 –15 27	4.56	69 –15 30	4.31
R angular gyrus/ supramarginal gyrus (TPJ)	42 -48 27	4.99 [2]	-	-	-	-
L precuneus	-6 -54 63	3.74	-	-	-	-
L precuneus	-12 -75 60	4.48	-	-	-	-
Temporal lobes						
L superior temporal cortex	-	-	-63 0 -12	4.15	-63 0 –9	3.46 [1]
L posterior superior temporal gyrus/ supramarginal gyrus (TPJ)	-54 -45 21	3.84 [2]	-	-	-	-
R posterior superior temporal gyrus (TPJ)	51 –42 24	4.40 [2]	-	-	-	-
L posterior superior temporal gyrus	-	-	-	-	-66 –15 9	4.24
R posterior superior temporal gyrus	-	-	66 –27 18	4.31	69 –27 9	4.30

If not indicated otherwise activations were thresholded at P<0.005, uncorrected; clustersize > 10 voxels
* All subtraction contrasts including congruent shape trials exclusively refer to the prespecified "critical congruent shape trials".
[1]Clustersize < 10 voxels
[2]This local maximum also occurred when this contrast was inclusively masked (cf., Material and Methods, pp. 52).
[3]Activation was thresholded at P<0.05, uncorrected

Table 3: continued

Regions	Behaviorally relevant oddballs vs. irrelevant oddballs		Irrelevant oddballs with reward association vs. irrelevant oddballs		Congruent shape trials with reward association vs. congruent shape trials*	
	MNI coordinates	Statistical effects (T-value)	MNI coordinates	Statistical effects (T-value)	MNI coordinates	Statistical effects (T-value)
Temporal lobes						
R superior temporal gyrus/ rolandic operculum	-	-	-	-	66 9 3	5.02
R superior temporal gyrus	45 18 -21	4.88	-	-	-	-
L middle temporal gyrus/ superior temporal gyrus	-63 -60 6	7.27	-	-	-	-
L inferior temporal cortex	-	-	-36 –3 -30	7.02	-	-
L inferior temporal sulcus/ inferior temporal gyrus	-54 -30 -18	4.44	-	-	-	-
L temporo-occipital cortex	-	-	-42 –39 -12	5.02	-42 –48 -9	4.03
Occipital lobes						
L middle occipital cortex	-	-	-39 –87 30	4.53 [1]	-45 –84 24	5.66
R superior occipital cortex/ cuneus	-	-	-	-	18 –99 12	3.82
L inferior occipital cortex	-12 -96 -18	3.72	-18 –102 -6	4.31	-	-
R gyrus fusiformis / inferior occipital cortex/ sulcus calcarinus	24 -72 3	3.91	39 –78 -3	5.76	30 –81 -6	4.01
Deep gray nuclei						
L/R thalamus	0 -33 -3	7.02	-	-	-	-
L superior colliculus	-3 –30 0	6.91				
L hippocampus	-	-	-36 –21 -18	6.68	-39 –21 -15	5.05
L amygdala/ gyrus ambiens	-27 3 -24	2.29 [3]	-27 3 -24	6.86	-15 3 –24	4.76 [1]
R amygdala/ hippocampus- amygdala complex	27 3 -24	3.98	24 –9 -18	4.66	30 –3 -18	3.29
R nucleus accumbens	-	-	6 3 -9	5.31	-	-
Cerebellum						
L cerebellar vermis/ cerebellum	0 –63 -6	3.59	-6 –63 -9	3.71	-	-

If not indicated otherwise activations were thresholded at P<0.005, uncorrected; clustersize > 10 voxels
* All subtraction contrasts including congruent shape trials exclusively refer to the prespecified "critical congruent shape trials".
[1]Clustersize < 10 voxels
[2]This local maximum also occurred when this contrast was inclusively masked (cf., Material and Methods, pp. 52).
[3]Activation was thresholded at P<0.05, uncorrected

the ones associated with behaviorally relevant oddballs presented in session 2 of the study by Gruber et al. (2006, in prep.). For that reason, the comparison between relevant oddballs and irrelevant oddballs was inclusively masked with the respective contrast from the prior study (cf., Material and Methods, pp. 52). The results of the masking procedure provided strong support for the assumption that activations in posterior OFC and frontoopercular cortices, but also in temporoparietal and postcentral cortices, were indeed attributable to the mere interaction of infrequency and behavioral relevance (see also: Table 3, pp. 64).

3.2 Effect of reward

The effect of reward was assessed by the following two comparisons:

  1.) [congruent shape trials with a reward association – congruent shape trials without a reward association] and

  2.) [all trials with an irrelevant oddball with a reward association – all trials with an irrelevant oddball without a reward association].

While the first contrast was intended to reveal activations that were associated with reward *per se*, the second one was sought to also uncover effects that were additionally caused by an interaction between infrequency and reward (i.e., the effect of an irrelevant infrequent distractor interacting with the effect of the positive hedonic value of a reward association) and was further intended to reveal common activations, which occurred for both congruent events in the shape task, that were associated with reward, and irrelevant oddball events with a reward association.

3.2.1   Congruent shape stimuli associated with a reward vs. congruent shape stimuli without a reward association

Activations associated with the effect of reward of frequent congruent shape events are listed in Table 3, column 3 (pp. 64). Orbitofrontal activations are further displayed on Figure 14C (p. 67). When congruent shape events were associated with a reward, significant activations were found in the left medial orbital gyrus and the right posterior olfactory sulcus. Furthermore, the reward association
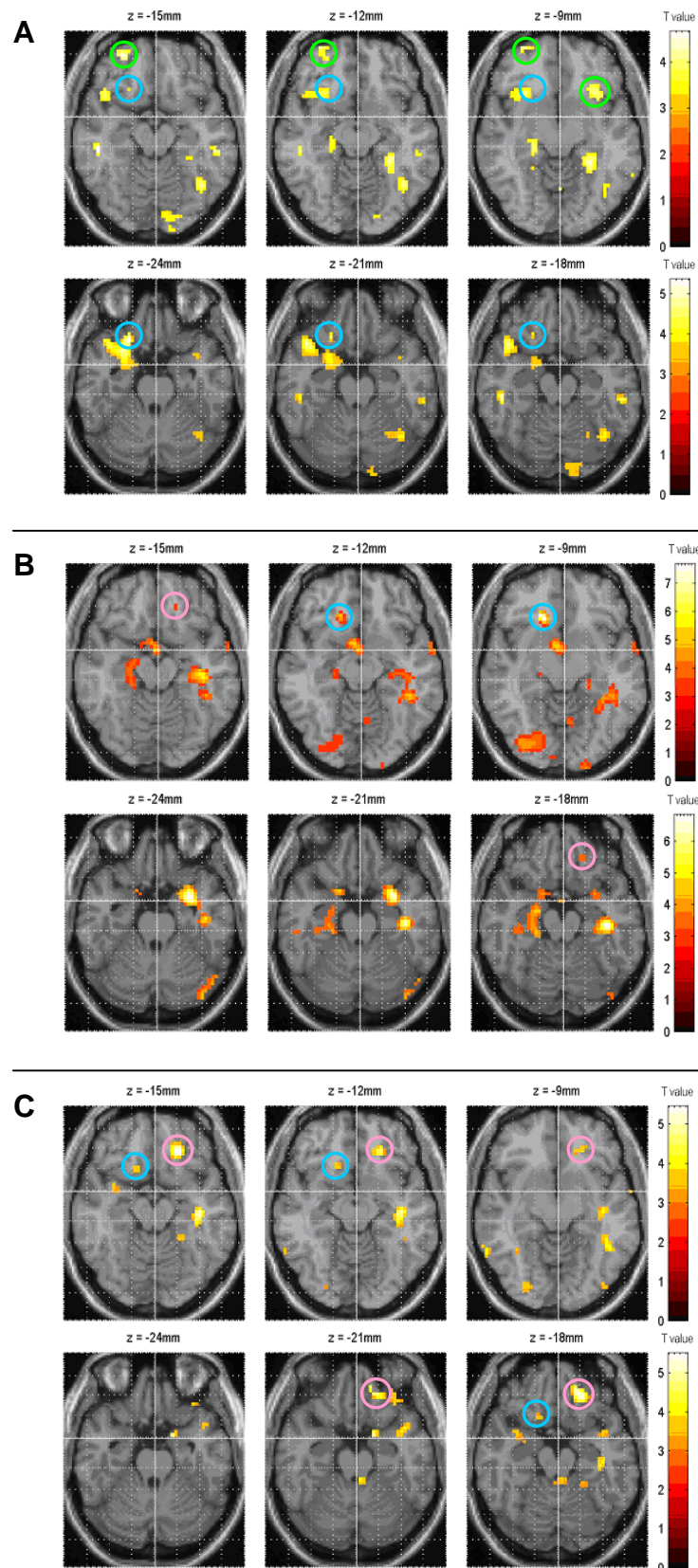
Figure 14: Orbitofrontal activations associated with different forms of motivational significance (at P<0.005, uncorrected). (A) behaviorally relevant infrequent events [behaviorally relevant oddballs versus irrelevant oddballs]; (B) infrequent stimuli with a reward association [irrelevant oddballs with a reward association versus irrelevant oddballs without a reward association]; (C) reward *per se* [congruent shape trials with a reward association versus congruent shape trials without a reward association]; blue circles indicate similar activations, that were detected in all three comparisons, green circles mark activations that occurred in association with behavioral relevance of infrequency, pink circles outline activations found in relation to the effect of reward in general; displayed in radiological convention on the standard MNI-template.

also activated the left amygdala (cf., Fig. 15A, this page) as well as posterior lateral parts of the right amygdala extending into the hippocampus-amygdala complex. Further, both the right and left posterior superior temporal gyri were activated by the reward association, however, not within the TPJ, and a significant activation in right postcentral cortex was also detected. Finally, the left hippocampus, the left temporo-occipital cortex and the extrastriate cortices were activated by reward *per se*.

3.2.2 Irrelevant infrequent stimuli associated with a reward vs. irrelevant infrequent stimuli without a reward association

Activations associated with reward in trials with an irrelevant oddball stimulus are listed in Table 3, column 2 (pp. 64). Orbitofrontal activations are further displayed on Figure 14B (p. 67). In correspondence to the orbitofrontal activations already observed for shape congruency with a reward association, the reward association presented in the context of an infrequent response-irrelevant stimulus activated left medial orbitofrontal gyrus. In addition, an activation within right posterior olfactory sulcus was also observed, which had already been detected in the previously reported reward contrast. The left postcentral gyrus exhibited two local maxima, which were not detected previously, while in the right hemisphere the postcentral activation maximum was almost identically to the one reported in the prior reward contrast. The
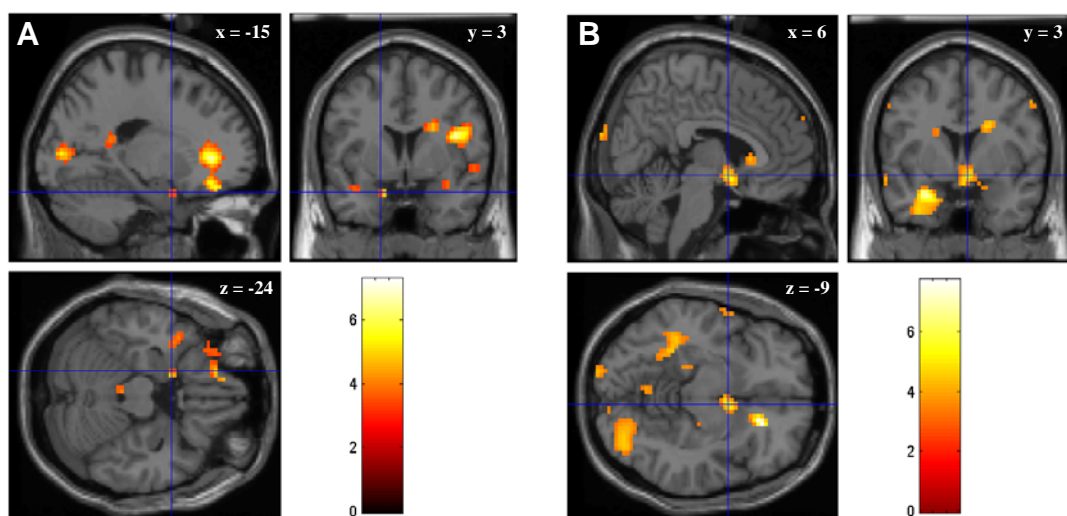
Figure 15: Activations of deep gray nuclei (P<0.005, uncorrected, marked by crosshairs). (A) activation of left amygdala by reward *per se* [shape congruency with reward association versus shape congruency]; (B) activation of right nucleus accumbens by irrelevant oddballs associated with reward [irrelevant oddballs with reward association versus irrelevant oddballs]; displayed in neurological convention on the starndard MNI-template.

left and right superior temporal cortices were also activated by irrelevant oddballs with a reward association. A local maximum in the left inferior temporal cortex was also detected in this comparison, but not in the previous reward contrast involving congruent shape trials. Further, activations in the left hippocampus and amygdala as well as the right amygdala and adjacent hippocampus-amygdala complex replicated the findings already made for the effect of reward *per se*. A local maximum in the nucleus accumbens was also observed in relation with an irrelevant oddball with a reward association (cf., Fig. 15B, p. 68), which was however not found in the previously reported reward contrast. In addition, significant activations within the temporo-occipital cortex and in visual-processing areas of the occipital cortex were also detected. Finally, the left cerebellum was significantly activated by irrelevant oddballs with a reward association.

3.3 Disparity in the neural response to different forms of biologically significant events

In order to test for significant differences with respect to the involvement of orbitofrontal subregions in the processing of different forms of salient behavioral relevance, experimental conditions of interest that were associated with a reward were directly compared to behaviorally relevant oddballs without a reward association. Accordingly, the following direct subtraction-contrasts were calculated:

1.) [congruent shape trials with a reward association – all trials with a behaviorally relevant oddball without reward association],

2.) [all trials with an irrelevant oddball with a reward association – all trials with a behaviorally relevant oddball without reward association]

In addition, the two opposite contrasts were also calculated. These contrasts compared all trials that included a behaviorally relevant but unrewarded oddball with either 3.) congruent shape trials with a reward association or 4.) all irrelevant oddball trials that were associated with a reward, which led to the two subtraction-contrasts:

3.) [all trials with a behaviorally relevant oddball without reward association - congruent shape trials with a reward association], and

4.) [all trials with a behaviorally relevant oddball without reward association - all trials with an irrelevant oddball with a reward association].
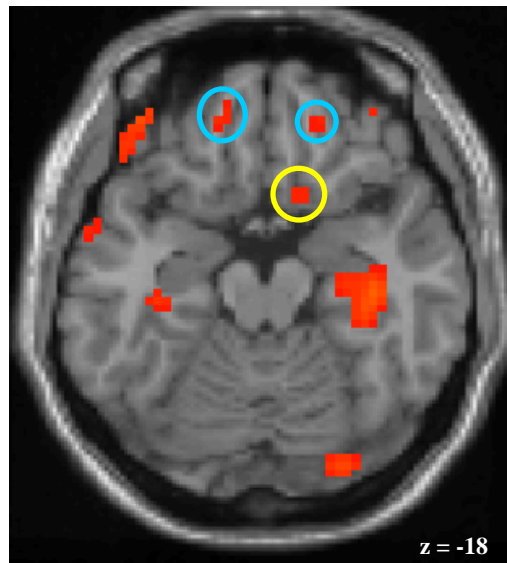
Figure 16: Activations selective for infrequent events with a reward association when compared to relevant oddball events without such an association. The yellow circle marks an activation focus in right posterior olfactory sulcus that already appeared at P<0.01, uncorrected, while the blue circles refer to activations in the medial orbital gyri, that only occurred at P<0.05, uncorrected. Activations displayed on figure are therefore thresholded at P<0.05, uncorrected and are shown in neurological convention on the standard MNI-template.

At the statistical threshold of $P < 0.005$, uncorrected, only one area in left medial OFC (coordinates (x y z): -15 36 –12, t = 3.29) was selectively activated by congruency associated with the chance to gain a reward when compared to behaviorally relevant oddball events without a reward association (comparison 1). This activation was almost identical to the local maximum observed in the left medial orbital gyrus in association with the effect of reward *per se* (cf., Table 3, column 3, pp. 64). In the reversed contrast (comparison 3) no orbitofrontal activity could be detected, but only the left cerebellum (coordinates (x y z): -9 –54 -33, t = 4.43) and the left postcentral cortex (coordinates (x y z): -60 –18 27, t = 3.39) where activated by behaviorally relevant oddballs without a reward association compared to shape congruency with a reward association.

When lowering the statistical criterion to $P < 0.01$, uncorrected, irrelevant oddballs associated with a reward led to a significant activation within right posterior olfactory sulcus when compared to behaviorally relevant oddballs (comparison 2; coordinates (x y z): 15 24 –12, t = 3.04; see also: Fig. 16, marked by yellow circle, this page). In addition, at $P < 0.05$, uncorrected, irrelevant oddballs with a reward association further activated an area in left medial OFC (coordinates (x y z): -12 45 –21, t = 2.12) in the direct comparison with relevant oddballs and there was also an activation in contralateral medial OFC (coordinates (x y z): 21 45 –18, t = 1.75) that was responsive to irrelevant oddballs with a reward association (see also: Fig. 16, marked by blue circles, this page). The activations in right olfactory sulcus and in left medial orbital gyrus were also detected in the previous comparison between irrelevant oddballs with a reward association and those without such an association,

which is displayed in Table 3, column 2 (pp. 64). In contrast, the activation in right medial orbital gyrus would have only been observed in the previous comparison of "irrelevant oddballs with a reward association versus irrelevant oddballs without such an association" (cf., Table 3, column 2, pp. 64), if the statistical criterion had been lowered to P < 0.05, uncorrected (coordinates (x y z): 24 48 –18, t = 1.78), and is therefore not listed in Table 3 (pp. 64).

The reversed contrast, in which trials with irrelevant oddballs with a reward association were subtracted from behaviorally relevant oddballs without a reward association also showed a selective activation in the cerebellum similar to the one described above (coordinates (x y z): -6 –57 -33, t = 4.65), but again no orbitofrontal activations could be detected.

Apart from orbitofrontal activations, congruent shape trials with a reward association further selectively activated superior temporal cortices bilaterally (coordinates (x y z): –69 –30 3, t = 3.98; coordinates (x y z): –63 –6 –9, t = 3.41; coordinates (x y z): 63 0 –6, t = 3.78; coordinates (x y z): 69 –30 6,; t = 3.26) and the hippocampi (coordinates (x y z): -33 –27 -15, t = 3.39; coordinates (x y z): 36 –18 -18, t = 3.28) when compared to trials with behaviorally relevant oddballs without a reward association.

Outside of the OFC, irrelevant oddballs with a reward association selectively activated occipital cortices (coordinates (x y z): -36 –96 0, t = 4.65; coordinates (x y z): 33 –84 -6, t = 7.33; coordinates (x y z): 15 –96 30, t = 3.82; coordinates (x y z): 30 –87 39, t = 3.67; coordinates (x y z): 27 –99 15, t = 3.28) at the statistical threshold of P < 0.005, uncorrected, when compared to unrewarded behaviorally relevant oddball events.

VI. Discussion

This study pursued the goal of assessing whether different forms of behaviorally relevant events – regardless of their actual rewarding properties – were processed by the OFC in a similar fashion or in a regionally distinctive way.

The key finding of the current study was that two directly adjoining clusters within right posterior OFC were activated by either reward or behavioral relevance of infrequency. However, even though reward and salient behavioral relevance both activated the right posterior OFC, the absolute activation maxima were not identical. Instead, the maximum for behavioral relevance of infrequency in the subtraction-contrast of "behaviorally relevant oddball events versus congruent shape trials" (coordinates (x y z): 21 21 -21; cf., Table 2, pp. 61) was situated directly adjacent (about 1-3 voxels in each direction) to the respective maxima for the two events associated with reward (congruency associated with reward: coordinates (x y z): 18 21 -15, irrelevant oddballs with reward association: coordinates (x y z) 18 24 -12; cf., Table 3, pp. 64), that were located in the posterior section of the olfactory sulcus, which may indicate that the two forms of behavioral relevance activated distinctive but still considerably close areas within posterior OFC. Further, the direct comparison between irrelevant oddballs with a reward association and behaviorally relevant oddballs revealed a stronger (or even distinct) activation located within the right posterior olfactory sulcus, which was not the case when congruent shape trials with a reward association were directly compared to behaviorally relevant oddballs. For that reason, it needs to be carefully discussed whether the right posterior orbitofrontal activations may be indeed interpreted in terms of the initial hypothesis according to which the posterior OFC was assumed to underlie a general monitoring mechanism that is involved in the processing of all forms of salient behaviorally relevant events.

In addition, other visibly distinctive coactivations within left medial OFC, right anterior OFC and lateral posterior OFC extending into frontoopercular cortices were also observed, which were either exclusively associated with reward or with behavioral relevance of infrequency (see Table 3, pp. 64). Still, a consistent and significant difference was only found for the left medial orbitofrontal focus in both direct comparisons between events with a reward association and behaviorally relevant oddball events. For that reason, it cannot be ruled out that the remaining

orbitofrontal activations in lateral posterior and anterior OFC in fact also represented candidate regions for the processing of salient behaviorally relevant events in general.

1. Behavioral data

In the following sections I will briefly discuss the behavioral data and the personality characteristics, before in a second step the neuroimaging findings will be addressed in detail.

1.1 Oddball events and behavioral performance

Responding to a behaviorally relevant infrequent event led to a significant increase in RTs and error rates, when compared to congruent shape trials and trials including an irrelevant oddball. However, processing of an irrelevant, distracting oddball stimulus did not exhibit such a detrimental effect on behavioral performance, even though the visual inspection of the data indicated an increase in RTs of about up to 50 ms when compared to congruent events in the shape task (cf., Fig. 9, p. 55).

In the empirical record, infrequent stimulus attributes have generally been assumed to consistently elicit an orienting reflex that also affects behavioral performance because the deviant stimulus attribute competes for cognitive processing resources with non-salient but actually relevant stimulus attributes. Infrequency *per se* was therefore expected to exert a detrimental effect on performance in the present study. For instance, in a prior study unexpected auditory pitch deviants, that were irrelevant for the behavioral response to be given, led to a significant increase in both RTs and error rates in an auditory target-detection task in which subjects had to respond to long duration tones (Sussman et al., 2003). Furthermore, this effect has also been observed to persist for several hundreds of milliseconds and could even significantly affect behavioral performance on the next trial (Escera et al., 1998). Linden et al. (1999) and Kirino et al. (2000) further found increased RTs for oddball-targets when compared to frequent standard events. In addition, Kirino et al. (2000) also reported the RTs for infrequent novels, that were also significantly prolonged when compared

to standard responses, even though subjects had to execute the same button press for novel like for standard stimuli. This further supports the assumption that infrequent deviance *per se*, regardless of its behavioral relevance or the infrequent response to be executed, generally should be expected to trigger an orienting reaction that has detrimental effects on behavioral performance.

In the current study, oddballs were presented in the same modality as the relevant stimulus feature shape (i.e., they occurred in the visual modality), but appeared in the currently irrelevant stimulus dimension color, which was similar to the study by Sussman et al. (2003). Both relevant and irrelevant oddball events were also considerably unexpected and deviant and therefore bore the potential of eliciting an orienting reflex which then had to be followed by a (re)direction of attention to the relevant task set which was necessary for correct performance in both oddball situations. It was therefore surprising to observe only a slight degradation in behavioral performance in irrelevant oddball trials. Nevertheless, most likely this may be explained by a striking difference in the presently applied experimental design when compared to the designs used in previous studies (e.g., the one of Sussman et al., 2003). Accordingly, in the current study participants got an extensive training before they were actually tested with the task-switching paradigm in the scanner which was intended to reduce error rates and improve overall performance. In contrast, in most prior oddball studies such a training was not necessary because task demands for infrequent target detection were extremely low and subjects were never required to switch between tasks (e.g., Sussman et al., 2003). Yet, the training-effect that improved performance in the current study might have been achieved at the expense of the behavioral measures of the orienting reflex, as the training might have helped participants to better overcome the orienting reflex behaviorally and even better ignore irrelevant oddball events, so that not every irrelevant oddball event actually led to a significant behavioral oddball effect (i.e., an increase in RTs). One support for this assumption were the considerably high standard errors observed for the mean RTs for irrelevant oddballs trials (cf., Fig. 9, p. 55), which exceeded both the standard errors of mean RTs for relevant oddballs and critical congruent shape trials.

1.2 Reward association and behavioral performance

Surprisingly, the reward association did not exhibit a significant influence on subjects' performance, even though participants were provided with a considerable incentive for good performance, a finding, which may be explained by different rationales: First of all, the competitive setting created in the current study required subjects to optimize their performance with respect to all trials that were associated with a reward. This was different from most previous reward studies in which monetary rewards were associated with performance in individual trials indicated by immediate reward-feedback. In these studies subjects' overall reward thereby consisted of the accumulated sum of individual rewards acquired within single trials in which the performance criterion was reached (e.g., Knutson et al., 2001b). For that reason, in these prior studies the reward value of an <u>individual</u> trial was probably by far higher than in the current study. Secondly, in the present study 50 percent of all trials were associated with reward (i.e., a reward association in every second trial) and trial succession was quite fast. In such a challenging situation one could imagine that subjects behaved strategically in that way that they tried to optimize their overall performance by responding as fast and as accurate as possible to every target regardless of its actual reward association. Finally, in the competitive situation created in the current study the performance of the other players was unknown to each subject. Against the background of the fast trial progression, subjects could have again used the above described strategy of optimizing responding to all targets in order to avoid missing a target with a reward association. If this was indeed the case, it might have also affected the neural reward response, as such a behavioral strategy would have entailed the risk, that the reward information might have been processed inadequately or even not at all. However, subjects were explicitly instructed to pay attention to the reward cues in advance and also exhibited neural activations within reward-sensitive regions (cf., Table 3, pp. 64), which indicates that the latter two explanations were rather unlikely.

1.3 Counterbalancing of oddball-color and finger mapping and behavioral performance

Slight or even significant differences with respect to response speed (RTs) and accuracy (rates of correct responses) were detected between the two color mappings (cf., p. 54). This finding may be interpreted in terms of a speed-accuracy trade-off that occurred rather incidentally as a result of inter-individual differences. That means, that some subjects simply increased response speed at the cost of response accuracy and *vice versa*. For that reason, it may be ruled out that the color mapping itself had an effect on overall performance on the group level.

Finally, the finger mapping did not affect behavioral performance, which was already expected because all subjects got an identical training in advance and had to get used to an experimental situation that was totally new to them.

2. Personality profiles

The individual personality profiles expressed by the TCI-scores of the participants were very variable. This was already expected, because the temperament model of Cloninger (cf., Richter et al., 1999) predicts that 17 different personality categories may be found in the population. Still, the mean scores of the four TCI temperament dimensions of all participants lay within the normal range (i.e., participants were only slightly above average in persistence, reward dependence and novelty seeking and slightly below average in harm avoidance) and therefore the sample was considered as representative for the healthy population.

The competitiveness scores were also considerably variable across subjects. Still, even subjects with quite low competitiveness scores performed well on the task. This might be explained by the fact that the task in the current study was not competitive in the sense of reacting directly to opponent's actions like for example in a game of chess or a bike race, but was rather competitive in the sense that a subject had to optimize its own performance unbeknownst of his/her opponents' performance. As the CI rather tests for direct <u>interpersonal</u> competitiveness (Houston et al., 1992), it

could have been inappropriate for the current study. Instead, it would have been better to measure subjects compliance and effort in responding to rewarded trials.

3. FMRI data

The present study pursued two working hypotheses. For this reason, the discussion of the imaging results will initially deal with the minor question, whether the current study using a one-session design achieved a replication of previous findings made by Gruber et al. (2006, in prep.), before in a second step the major hypothesis of the current study will be addressed. It thereby will be discussed whether posterior OFC may be indeed assumed to generally represent motivationally significant salient stimuli. In addition, the discussion will also address complementary orbitofrontal functions in the representation of positive hedonic value and violations of expectations. Finally, the remaining activations, that occurred partly selectively in association with either reward or behavioral relevance of infrequency, will also be discussed.

3.1 Replication of previous results – Working hypothesis (1)

The first but minor intention of this study was the replication of the results from a previous study from my laboratory (Gruber et al., 2006, in prep.). Therefore, an inclusive masking procedure was applied (for a detailed description of this masking procedure please see: pp. 52).

Altogether, the current study replicated some, but not all activations that had been found to be selectively activated in the context of behavioral relevance of infrequency of the previous study (cf., Table 4, p. 79). Among them were activations within bilateral posterior OFC and adjacent frontoopercular cortices. Thus, it can be ruled out, that the orbitofrontal activations detected in the previous study were simply a result of the instruction-reversal concerning the infrequent deviant, which in the first session had to be ignored by the subjects and in session 2 became a prospective memory target on which subjects had to respond accordingly (for a short review on the design of the previous study please, see also: p. 29). The present study

did not include such a reversal confound as both irrelevant and relevant oddballs were presented within the same session and did not change their response-associations throughout the course of the experiment.

Moreover, the prior study further reported an activation focus within anterior OFC, which would have conformed to the one reported in the present study if it was not located in the opposite hemisphere (see also: Table 3, pp. 64). The present study also replicated activations within left and right parietal cortices (e.g., supramarginal gyrus) also covering the temporoparietal junction area, regions that were also found in the previous study. In addition, the current study further revealed an activation focus that lay within left superior colliculus, whereas Gruber et al. (2006, in prep.) found a local maxima in the right superior colliculus. Since the cluster observed in the present study also extended into the right superior colliculus, it may nevertheless be viewed as a replication of the previous observation.

However, the remaining activations, especially those within the cingulate cortex as well as the superior frontal and temporal cortices reported in Table 4 (p. 79), were not replicated at the presently applied statistical threshold of $P < 0.005$, uncorrected, which may at least partly be assigned to design-related differences, differences in duration of the training or the overall lower statistical power of the present study. For instance, by not separating irrelevant and relevant oddball events by different sessions, the present study might have entailed the risk that subjects treated all infrequent events in a similar way or used a strategy in which they tried to block out deviant information to be able to respond as fast as possible to events with a reward association. An alternative explanation might be seen in the fact, that in the prior study participants had no chance to train the manual response to the relevant oddballs in advance, but instead got the new instruction how to change their behavior in response to the infrequent white color in the shape task in the break between session 1 and session 2. For that reason, the oddball event was probably perceived as more salient and possibly required a higher degree of cognitive control to ensure correct execution of an untrained and therefore novel response to a formerly ignored stimulus. It may thus be speculated that the requirement to respond to the previously ignored infrequent deviant in the second session of the study by Gruber et al. (2006, in prep.) led to activations that represented overall learning effects (e.g., learning of a new stimulus-response association) or higher cognitive and behavioral demands,

Table 4: Comparison of activations found in Gruber et al. (2006, in prep.) and those for behavioral relevance of infrequency detected in the present study

Region	Coordinates from the study of Gruber et al. (2006, in prep.) in the contrast: Behaviorally relevant oddballs versus irrelevant oddballs [1,2]		Coordinates from the present study that conform with those from Gruber et al. (2006, in prep.) in the contrast: Behaviorally relevant oddballs versus irrelevant oddballs	
	MNI coordinates	Statistical effects (T-value)	MNI coordinates	Statistical effects (T-value)
Frontal lobes				
R superior frontal gyrus	-4 20 64	5.79	-	-
L anterior orbital gyrus / lateral orbital gyrus	-28 52 -16	6.56	-	-
L frontoopercular cortex	-36 20 0	9.90	-36 18 -3	5.23
R posterior orbital gyrus/ frontoopercular cortex	32 28 -12	10.89	30 21 –9	4.04
R posterior orbital gyrus	32 24 -24	6.12	27 18 -27	6.07
R cingulate sulcus / middle cingulate cortex	4 28 40	11.48	-	-
Parietal lobes				
L postcentral cortex	-64 –32 24	6.40	-66 -18 27	14.75
L supramaginal gyrus/ posterior superior temporal cortex (TPJ)	-60 –56 36	11.59	-54 -45 21	3.84
R supramarginal gyrus (posterior part)/ posterior superior temporal cortex (TPJ)	64 -48 28	17.89	-	-
R angular gyrus/ supramarginal gyrus/ posterior superior temporal cortex (TPJ)	48 -48 36	13.02	42 -48 27	4.99
	56 –44 32	9.19	51 –42 24	4.40
R superior parietal lobule	52 -52 52	8.27	-	-
Temporal lobes				
R superior temporal gyrus	28 12 -32	6.48	-	-
R inferior temporal gyrus	60 -40 -20	5.73	-	-
L inferior temporal gyrus	-52 -24 -32	5.50	-	-
Deep gray nuclei				
L/R colliculi superior	4 -28 -12	6.56	-3 –30 0	6.91
Cerebellum				
L Cerebellum	-40 -48 -36	5.99	-	-

[1] Activations are reported at P<0.05, corrected for FWE

[2] Subtraction contrast: [behaviorally relevant low-frequency events (Session 2) – irrelevant low-frequency events (Session 1)] inclusively masked with the contrast [behaviorally relevant low-frequency events (Session 2) – behaviorally relevant events with normal frequency (Session 3)]

which were not present in the current study as subjects got the opportunity to practice the task in advance. Interestingly, the present study also led to new activation foci which were mainly located in occipital and inferior temporal regions along the visual "what-processing" pathway (cf., Borowsky et al., 2005). This may again be attributed to design-related differences (i.e., the presently applied one-session design) since in the current study subjects were required to differentiate between response-relevant and irrelevant oddball events by their color, which even could have led to an increase in visual salience of the relevant oddball color. Conversely, in the previous study the three-session design did not require such a differentiation because relevant and irrelevant oddballs were presented in different sessions. This may explain why a differential response in regions of visual object processing was detected when compared to the previous study.

In sum, the applied masking procedure allowed for the inference that the above reported activations and in particular those in posterior OFC were indeed associated with infrequent events that were also relevant for the organism's behavior and had not simply occurred as the results of the instruction-reversal between session 1 and 2 in the previous study by Gruber et al. (2006, in prep.). It was therefore feasible to accept the first working hypothesis, that the OFC was indeed activated by infrequent events that required a behavioral adjustment. Nevertheless, the detection of a subthreshold orbitofrontal activity in conditions including an irrelevant oddball event in the present study (cf., Table 1, p. 59) challenged the selectivity of the posterior orbitofrontal response for behaviorally relevant oddball events which was initially predicted from the results of the prior study of Gruber et al. (2006, in prep.). The following section will carefully address this issue and will derive a probable explanation for its occurrence in the context of infrequency *per se*.

3.2 The orbitofrontal cortex and processing of behaviorally irrelevant deviance

Surprisingly, in the present study the right posterior and also the anterior orbitofrontal cortex exhibited subthreshold activations in association with irrelevant oddball events (cf., Table 1, p. 59) with almost identical local maxima as those reported for behaviorally relevant oddballs (cf., Table 2, pp. 61). This finding was

not predicted from the results of the prior study from Gruber et al. (2006, in prep.), which did not observe an orbitofrontal response to irrelevant infrequent deviance. On the first view, this current observation could have indicated that the orbitofrontal cortex subserved processing of unexpected visual deviance in general, even if the deviant information was irrelevant for the organism. And indeed, one previous study also observed similar orbitofrontal activations in both right posterior and anterior orbitofrontal cortex that were associated with the mere observation of irrelevant deviant stimulus features, which occurred unexpectedly in the visual display, but were not relevant for the organism since they did not require a button press (Petrides et al., 2002). Nevertheless, if orbitofrontal activations would indicate that such a general mechanism indeed existed, why had similar orbitofrontal responses to irrelevant visual deviance (i.e., to irrelevant distractors and novels) not shown up in other oddball studies and especially in the previous study of Gruber et al. (2006, in prep.)? One might answer this question by the fact that in the previous study by Gruber et al. (2006, in prep.) an experimental manipulation was used in which every deviant stimulus presented in session 1 was irrelevant for the behavioral response to be given. Instead, in session 1 of their study subjects were required to immediately reorient attention from the irrelevant deviant oddball color to the relevant shape dimension and to respond to the respective shape. For that reason, no further processing of the deviant color (e.g., an evaluation of the behavioral relevance of the oddball color) was necessary. This was different from the less controlled design used by Petrides et al. (2002), in which subjects passively viewed normal and deviant stimuli in succession, but were not involved in any attentionally demanding task. For that reason, it cannot be ruled out that the participants in the study of Petrides et al. (2002) evaluated the strongly visually deviant (and sometimes even novel) stimulus features with regard to their behavioral relevance or even assigned some kind of relevance to them, because they were not explicitly instructed to refrain from doing so. In my opinion, the inference on the data offered by Petrides et al. (2002), according to which the orbitofrontal activations observed were simply a correlate of deviance detection, was therefore not warranted. Instead, I would infer that the orbitofrontal involvement in deviance processing in that particular study rather indicated that this region actually subserved the processing of salient and (potentially) relevant events in the environment.

With regard to the present results, it may therefore be very likely that the similarities in orbitofrontal activation for both relevant and irrelevant oddballs were also a result of the applied experimental design. For one thing, the one-session design used in the present study required subjects to differentiate between irrelevant and relevant oddballs within the same session. This made it necessary that subjects evaluated every infrequent event they encountered with respect to its behavioral relevance, which was not required in the previous study by Gruber et al. (2006, in prep.) who had presented irrelevant and relevant oddballs in separate experimental sessions. In addition, the one-session design used in the present study further entailed the risk that subjects could have wrongly assigned the behavioral relevance attribute to most infrequent events they encountered and not only to behaviorally relevant events. The assignment of behavioral relevance to most infrequent events in the present study could have thereby already occurred preattentively, before in a second step the actual relevance of the event was consciously revised. Finally, another possible explanation could be derived from the perceptual similarities of the two oddball colors white and yellow used in the current study. Due to the strong light-dark contrast against the black screen the two light colors white and yellow might have been perceived as highly similar leading to a reduced differentiability of infrequent oddball colors at least in some trials, which could have even facilitated an accidental misattribution of the behavioral relevance attribute to some of the irrelevant oddball events.

Due to the above-presented reasons, I therefore consider the orbitofrontal activations observed for irrelevant oddballs as mainly being a result of the experimental design employed in the present study. Orbitofrontal subthreshold activations in response to irrelevant deviance and the OFC may therefore probably not be considered as underlying infrequency processing *per se*, but rather represented either a general evaluation of behavioral relevance of all salient events occurring in the neuropsychological experiment or an accidental assignment of behavioral relevance to most salient stimuli subjects encountered in the current study. This would also mean, that in the remaining sections of the discussion, the subthreshold orbitofrontal activations that occurred in relation to irrelevant oddballs will be treated as if they were actually not present at all (like in session 1 of the study by Gruber et al., 2006, in prep.), which will of course also affect the subtraction contrasts involving both oddball types. In the contrast presented in Table 2 (pp. 61) behaviorally relevant

oddballs compared to congruent shape trials activated a region within right posterior orbitofrontal cortex (coordinates (x y z): 21 21 –21, t = 5.07) that was quite similar to the one found in the subtraction contrast involving the comparison of irrelevant oddballs versus congruent shape trials (cf., Table 1, p. 59; coordinates (x y z): 18 21 –21, t = 2.69). Following the logic of subtraction contrasts in SPM, in the direct contrast between behaviorally relevant oddball stimuli and irrelevant oddballs presented in Table 3 (pp. 64) this local maximum naturally did not show up, because it had also been found to be activated <u>to a similar degree</u> in association with irrelevant oddballs. However, since the orbitofrontal activations related to irrelevant oddballs were assumed to be rather a function of the experimental design and not of infrequency processing *per se*, in the upcoming discussion this posterior orbitofrontal cluster maximum will therefore be also assigned to processing of behavioral relevance of infrequency.

3.3 Comparing different forms of biologically significant events – Working Hypothesis (2)

The results of the current study indicate that, in line with the second working hypothesis, the right posterior OFC was indeed responsive to different forms of salient behaviorally relevant events. However, despite this similarity in the right posterior orbitofrontal response, activations in the remaining orbitofrontal subareas (including more lateral parts of the posterior OFC) rather appeared to be selective for either behaviorally relevant oddballs or reward *per se*. This means, that hypothesis (2A) also had to be accepted. In this section it will be discussed how the present findings may be interpreted within the general framework of orbitofrontal function.

Apart from the OFC, different types of biologically significant stimuli activated other brain regions. These regions comprised both brain areas that were responsive to motivational significance (e.g., amygdala) or reward (e.g., nucleus accumbens), as well as parts of the "adaptive reflexive processing network" (Kiehl et al., 2005a) including temporal, parietal and occipital cortices. Most of these regions showed to be selective for either behavioral relevance of infrequency or reward. The discussion will also address coherent explanations for these observations.

3.3.1 The right posterior orbitofrontal cortex – Involvement in processing of different forms of behaviorally relevant events?

In the current study, both behaviorally relevant oddballs and events with a reward association activated a similar part of **right posterior OFC** (located near or within the right posterior olfactory sulcus; cf., Table 2, pp. 61; Table 3, pp. 64). Considering the rationale of the present study (cf., pp. 27), this finding may be interpreted as evidence for a general mechanism that is involved in the processing of significant events in the environment. Events with a reward association represented a motivational goal and were probably perceived as highly significant, because accurate and fast performance in these trials enhanced the chance to gain the additional award. Similarly, the relevant oddball trials were also highly significant due to the requirement to rapidly adjust attentional and behavioral resources towards an unexpected, but behaviorally relevant event. It may therefore be assumed that both rewarded events and behaviorally relevant oddballs shared the common property of being relevant to the organism and were probably assigned priority in being processed, regardless of the actual behavioral consequences (i.e., the rapid motor adjustment) or the associated hedonic feelings that followed these events.

Previous findings also provided support for the assumption that the posterior OFC represented motivationally significant events that were of (potential) relevance to behavior. For instance, a similar posterior orbitofrontal subregion has been shown to be sensitive to stimuli with a positive reward-value and a high incentive motivation like food stimuli in a food-deprived state (O'Doherty et al., 2000; Gottfried et al., 2003). Another study observed an orbitofrontal response to the anticipation of the oral delivery of a glucose solution when compared to oral delivery of either a neutral or a saline solution (O'Doherty et al., 2002). However, with regard to the present findings an interpretation including only positive valent stimuli would have been too restricted as presently both events with a positive value (i.e., events with a reward association) and neutrally valenced behaviorally relevant oddball events activated a similar posterior orbitofrontal subarea. And indeed, this posterior orbitofrontal subarea was not exclusively activated by positively valenced stimuli in previous studies. In a study using both appetitive and aversive olfactory conditioning the authors reported a right posterior orbitofrontal activation – amongst further rostral activation foci – which was associated with valence-independent olfactory learning

in conditioning (Gottfried et al., 2002). The posterior OFC thereby represented both aversively and appetitively valenced olfactory events (i.e., 5% 4-methyl-pentanoic acid and 8% vanillin), but was not activated by a neutrally valenced odor (i.e., the presentation of 0.1% phenethyl alcohol). Interestingly, this posterior orbitofrontal focus corresponded to the respective orbitofrontal activation, that has been reported to be responsive to high incentive value of food-related stimuli in a food-deprived state, observed in the olfactory devaluation study of Gottfried et al. (2003; see also: Fig. 3B, p. 28). Since the reinforcer devaluation paradigm used by Gottfried et al. (2003) did not include a strongly aversive condition (e.g., a disgust-inducing food-related odor), one cannot rule out that strongly aversive events could have also activated posterior OFC to a similar degree as the high incentive food-related odors when presented in a food-deprived state. In addition, another study also reported an activation in the left posterior olfactory sulcus (coordinates (x y z): -16 28 -18) that was correlated with the degree of subjectively perceived unpleasantness as expressed by a rating scale when participants were presented with 6 different non-food odors, while pleasantness ratings was exclusively represented by anterior-medial OFC (Rolls et al., 2003). Superficially, this finding seems to contradict the one reported by Gottfried et al. (2002; see above), because it pointed to a valence-dependent representation within OFC, according to which pleasantness was coded rather anterior-medially, while aversiveness was mainly represented posteriorly within the OFC. Still, when we take a closer look at the design, there might be an alternative interpretation: Considering the fact that the unpleasant odors were all related to different acids, these events should bear a stronger significance for the organism than the pleasant floral and woody non-food odors that were used by Rolls et al. (2003). Acid smell may be perceived as particularly noxious and strongly aversive, which in a real-world environment should trigger active avoidance behavior to evade the danger of being injured. In contrast, pleasant odors should not at any case elicit approach behavior. In the study of Rolls et al. (2003) the pleasant odors did not indicate the presence of food and were therefore considerably unimportant for the individual's needs and its survival. Conversely, Gottfried et al. (2002) used the food-related odor of vanillin which should have been more relevant to the individual as this odor in everyday life often predicts the presence of a food item. Finally, considering the results from the meta-analysis by Kringelbach and Rolls (2004; see also: Fig. 1, p. 21), which also pointed to a valence-independent representation of

reinforcers in posterior parts of the orbitofrontal cortex, one may indeed infer that the right posterior orbitofrontal subregion detected in the present study also represented behaviorally relevant events independent of their actual valence.

Interestingly, a significant orbitofrontal activation in right posterior orbital gyrus and adjacent parts of the olfactory sulcus has also been observed in a situation in which subjects made a conscious decision on target detection in a dichotic listing task. This was in so far astonishing as this activation rather varied with the <u>subjective decision</u> on target presence in a situation of uncertainty created by dichotic listening, than with physical target presence itself (Pollmann et al., 2004). This further leads to the assumption, that this orbitofrontal subregion may be assumed to represent a self-referential process which allows for the conscious processing of significant events and voluntary (behavioral) decision-making even in ambiguous situations. In the current study, both rewards and behaviorally relevant oddballs represented motivational goals that required conscious processing to enable an enhancement of cognitive resources and successful behavioral performance. Especially the behaviorally relevant oddball events could only be processed adequately, after they had been consciously perceived and subjects decided upon their presence. Similarly, optimization of performance in trials with a reward association also required conscious processing of the reward cue that contained the important information on their incentive value.

Finally, one important issue that has not been addressed so far is, that irrelevant oddballs with a reward association led to a quantitative difference (i.e., a stronger BOLD response) in the activation of the right posterior OFC when directly compared to behaviorally relevant oddballs, while congruent shape trials with a reward association did not when being directly compared to behaviorally relevant oddballs (cf., Results, pp. 69). It is most likely, that in case of irrelevant oddballs with a reward association the combined effects of the design-related subthreshold activations in posterior OFC elicited by irrelevant oddballs *per se* and also those attributable to the incentive motivation of the reward association in itself increased the activation in the posterior OFC to a degree that significantly exceeded activations due to the mere effect of salient behavioral relevance in relevant oddball trials <u>without</u> an association with the chance to gain a reward. This would also explain why in the direct comparison between congruent shape trials and trials including

behaviorally relevant oddballs, no such significant difference in activation in right posterior OFC could be observed (even not when lowering the statistical threshold to P<0.05, uncorrected) and would again strongly argue for a similar coding of motivational/ behavioral relevance within an identical subregion of right posterior OFC in these two experimental conditions.

In sum, the present results provide first support for the inference that right posterior OFC represents highly significant environmental events regardless of their actual valence. This observation is also supported by prior results from the studies discussed above and a recent meta-analysis by Kringelbach and Rolls (2004; see also: Figure 1, p. 21). Still, the present results further show that an association with a pleasant or aversive event is no necessary prerequisite to activate posterior OFC, but instead the mere verbal instruction to adjust ones behavior to an unexpected deviant seems to be sufficient to create a "cognitive incentive" that acquired motivational significance and thereby became a behavioral goal. I would therefore infer that this particular posterior orbitofrontal subregion near the posterior part of the olfactory sulcus may be indeed assumed to be responsive to any form of behaviorally – or more generally speaking – motivationally significant stimuli in the environment, with the restriction that the respective environmental stimuli also need to be considerably salient in the context in which they appear.

3.3.2 Selective coding of behavioral relevance of infrequency within posterior and anterior OFC – Violations of expectation and voluntary goal-change

Apart from the right posterior orbitofrontal activation discussed above, I also detected coactivations in more **lateral parts of the posterior orbitofrontal cortices** that further extended into the **frontal opercular cortices** (cf., Table 3, pp. 64). These coactivations were associated with the unexpected occurrence of behaviorally relevant oddball events, but did not show up in the reward contrasts. A smaller **right anterior orbitofrontal focus** was also exclusively detected in association with behaviorally relevant oddballs in the present study. Still, the direct contrasts of behavioral relevance of infrequency against trials with a reward association did not

reveal these distinctive coactivations in response to behavioral relevance of infrequency, which does not allow for a final conclusion on their selectiveness.

And indeed, considering previous studies that reported activations in similar parts of the posterior OFC and adjacent parts of anterior insular and frontoopercular cortices, one may assume that this lateral posterior orbitofrontal subregion also had been especially responsive to stimuli with a high incentive value or more generally speaking with a high motivational significance. For instance, in male subjects left lateral posterior OFC has been observed to be responsive to facial beauty particularly to that of female faces when compared to male ones (Aharon et al., 2001). In addition, highly motivating reinforcers (monetary reward), when compared to less motivating but nevertheless positive incentives (verbal feedback), also led to an increase in activation of the posterior orbitofrontal cortex (Kirsch et al., 2003). Further, a valence-independent representation of highly significant and arousing environmental stimuli has also been observed in lateral posterior orbitofrontal subareas. This was for instance the case, when a reward was either received in the context of a winning streak or when a penalty occurred in the context of accumulating loss (Elliott et al., 2000a) or when subjects received either the best or worst possible outcome in a gambling study (Breiter et al., 2001).

Still alternatively, one may treat these lateral posterior orbitofrontal coactivations, that further extended into the frontal operculum, as <u>selective for behaviorally relevant oddball events</u>, since the overall low statistical power of the whole fMRI results could have obscured the detection of these selective activations in the direct contrasts. In doing so, one then has to consider another important theory on OFC function, which has not been addressed so far. According to O'Doherty et al. (2003) the OFC has not only been implicated in coding stimulus reward value, but is presumably also involved in <u>behavioral control</u> after rewarding or punishing feedback. By constantly monitoring the internal and external environment for possible changes, the OFC has been assumed to give a sort of running commentary on values of the expected outcome associated with particular actions (Schoenbaum & Setlow, 2001). More importantly, upon the detection of violations of expectations with regard to predicted outcomes, the OFC has been assumed to provide the decisive information on the change in the behavioral relevance or motivational significance of a stimulus, which is vital for the implementation of an adaptive behavioral change (O'Doherty et al., 2001, 2003). Indeed, most reversal-learning

studies, in which subjects had to reverse responding to a previously rewarded stimulus after they had consistently experienced violations of their expectation in form of a negative feedback (see also: Introduction, pp. 19), observed lateral posterior orbitofrontal activations (partly extending into the anterior insular cortex). These activations showed to be selective for the <u>final reversal error</u> which led to the actual behavioral change (Cools et al., 2002; Kringelbach & Rolls, 2003; O'Doherty et al., 2003) and were close to the lateral posterior clusters found in the current study. O'Doherty et al. (2003) interpreted these activations as reflecting the detection of a change in reward contingencies or, even more specifically, a decrease in the average reward value of the currently chosen stimulus that triggered a reversal in stimulus choice. The authors were further able to rule out that the lateral posterior orbitofrontal activation was simply attributable to the inhibition of responding. Their design also included a condition in which subjects only observed the stimulus selection made by the computer, but still O'Doherty et al. (2003) found the same posterior orbitofrontal activation to be associated with the final reversal error after which the computer actually changed stimulus choice.

In light of these prior findings it is therefore possible to adequately account for the **lateral posterior orbitofrontal** activations, if one considers them as selective for situations in which a behaviorally relevant oddball required a behavioral adjustment. Accordingly, the experimental setting of the present study created a context in which the majority of the shape-cues validly cued the shape task. For that reason, subjects probably built up the overall expectation that a shape cue was also followed by a shape task on most occasions. However, infrequently and therefore <u>unexpectedly</u> the behaviorally relevant oddball color occurred within the shape task and made the preceding shape cue invalid. More importantly the oddball color immediately required the rapid reversal of the already prepared stimulus-response mapping of the shape task set to that of the relevant oddball color. It is important to note, that in the current study it was not the unexpected punishing feedback like in most common reversal-learning studies, but – more generally – the actual violation of an expectation (i.e., the expectation of a shape task following the shape cue) followed by a <u>rapid voluntary change in the behavioral goal</u> towards the unexpected event which supposedly activated lateral posterior OFC. In the previous study from my laboratory (Gruber et al., 2006, in prep.) it had already been demonstrated that the <u>frequent</u> presentation of a behaviorally relevant stimulus, that required the same

behavioral adjustment as the <u>infrequent</u> behaviorally relevant oddball stimulus presented in the current study, which was however well practiced, did not activate the OFC. That means, that the detection of an infrequent and unexpected behaviorally relevant event that also required a rapid change in goal-directed behavior (i.e., the interaction between infrequency and behavioral relevance), was a necessary prerequisite for activation of the lateral posterior OFC. Since adjacent parts of the **frontoopercular cortices** were also activated by behaviorally relevant oddballs, one may further infer that this region could have complemented orbitofrontal function by representing a memory function in the sense of a "<u>retrieval mode</u>" that compared incoming sensory information with a stored template (Rugg et al., 1999; Bledowski et al., 2004) and therefore facilitated the specification of salient environmental stimuli as prospective memory targets (i.e., relevant oddballs), which further assisted the <u>correct</u> behavioral adjustment (i.e., the actual reversal of the stimulus-response association).

Finally, one should not overlook the **right anterior orbitofrontal cluster** that was also coactivated by behavioral relevance of infrequency in the present study. Similar activations within lateral anterior orbitofrontal cortex have also been found in one reversal-learning study, when subjects reversed stimulus choice upon the <u>final reversal error</u> (O'Doherty et al., 2001), and further occurred in another study that used <u>invalid</u> temporal and spatial cues (Nobre et al., 1999), which indicates that the anterior orbitofrontal activation may have been somehow linked to the behavioral reversal and the lateral posterior activations observed in the present study.

If we also consider the fact that the above discussed posterior activation clusters and the right anterior cluster observed in the present study were located quite laterally within the OFC, it is tempting to follow the proposals made by other researchers (O'Doherty et al., 2001; Elliott et al., 2000b; Kringelbach & Rolls, 2004) and assume a rather medial-lateral dissociation of orbitofrontal functioning. According to these researchers, lateral orbitofrontal parts were mainly reported to be associated with situations in which expectations were violated (mostly by punishing feedback) and necessitated a rapid behavioral change, while medial parts rather presented processing of positive incentives. In the present study, orbitofrontal foci that were selective for behavioral relevance of infrequency were indeed located more laterally, while reward activated rather medial parts. Further, following the neuroanatomical hierarchy within OFC (Öngür & Price, 2000) according to which posterior regions

converge on anterior subareas, in the present study one might even speculate that posterior and anterior OFC could have somehow "communicated" to permit more complex information processing and decision-making (see also: Kringelbach, 2005).

However, for reasons that have been outlined above (i.e., the lack of statistically significant differences in activations in these regions when directly comparing different types of biologically significant events, cf., pp. 69), I cannot unequivocally infer that coactivations in lateral posterior and right anterior OFC were selective for behavioral relevance of infrequency, even though prior evidence strongly supports their selectivity for the response-reversal following unexpected and significant changes in stimulus-response association. For that reason, the above offered interpretations can only be preliminary and future studies have to carefully address this issue to allow a clear inference.

3.3.3 Reward processing, positive hedonic value and the medial orbitofrontal cortex

In the present study, events with a reward association selectively activated **left medial orbital gyrus** (cf., Table 3, pp. 64), which indicates that rewarded events might have carried some inherent property that was not innate to behaviorally relevant oddball events. If one assumed that every rewarded event automatically triggered positive emotions (i.e., feelings of pleasure), one might hypothesize that it was the positive hedonic value or pleasure associated with the reward association that selectively activated the medial orbitofrontal cortex in the current study. Indeed, reward processing is not only processing of biologically significant events that have acquired a motivational value, but also includes processing of positive hedonic value. Based on neurobiological findings, Berridge and Robinson (2003) proposed a clear dissociation between the "wanting" and the "liking" components of reward, that in most occasions occur together in a real world environment. According to them, the processing of incentive salience or the perception of "cognitive incentive goals" represents the motivational consequences of positive reinforcers (i.e., the "wanting" component). Instead, the unconscious processing of "liking" and the conscious pleasure experienced from a reward have both been assumed to represent the

affective consequences of reward. In other words, while "liking" of a reward describes the hedonic experience associated with reward, the "wanting" component is rather tied to its behavioral significance in the sense of the motivation to approach and consume the reward. Interestingly, "wanting" and "liking" have been found to be mediated by different neural systems (e.g., "wanting" has been reported to be mainly influenced by dopamine neurotransmission, which has however no association to the "liking" component; for a more elaborate overview supporting this dissociation please cf., Berridge & Robinson, 2003), which would point to the possibility that these different components could in fact be also represented by different orbitofrontal subareas.

The OFC has been shown to represent both pleasurable and motivationally significant stimuli like winning money (e.g., Thut et al., 1997), pleasant odors (e.g., Rolls et al., 2003), sweet taste (e.g., O'Doherty et al., 2002), facial beauty (Aharon et al., 2001) and pleasant touch (Francis et al., 1999). Unfortunately, most of these studies did not allow for a clear dissociation between motivation and pleasure. If for example Gottfried et al. (2003) manipulated the hunger state and therefore the motivation of their participants, the consciously perceived pleasantness and therefore supposedly also the hedonic experience associated with the food-related odors were naturally also manipulated. In fact, Gottfried et al. (2003) did not exclusively observe the above described activations in posterior orbitofrontal cortex, but further detected additional maxima in left and right anterior medial OFC that were responsive to both learning of stimulus-reward associations and the appetitive value of food-related reinforcers. These activations partly overlapped with the cluster in left medial orbital gyrus detected in the present study. Even though, this might indicate that medial parts of the OFC could have indeed coded positive reward value and the pleasantness of reward, a clear identification of positive valence is only possible, if one directly compares two motivationally relevant events of contrasting valence. A study (O'Doherty et al., 2001) that contrasted reward leading to a financial gain with punishment involving a financial loss, reported a significant association between reward and activity within medial parts of the OFC that were also partly close to the left medial orbitofrontal maximum detected in the current study. This activation was interpreted in terms of representing a monitoring function for the rewarding consequences or the value of a currently chosen stimulus (O'Doherty et al., 2001). Still, the medial orbitofrontal activation was not found in relation to punishment and

might therefore be rather attributable to the positive hedonic value of a rewarded event. This assumption has been also supported by another observation made by O'Doherty (2003) who observed a medial orbitofrontal activation to be sensitive to reward valence, while adjacent and further anterior parts of the medial OFC along the midline of the human brain were rather involved in behavioral choice in the sense of response maintenance within the applied reversal-learning paradigm. I would therefore conclude that the assumption made by for instance Elliott et al. (2000b) or O'Doherty et al. (2003), according to which medial OFC generally subserved a maintenance of currently applied response strategies and of stimulus-response associations, was not always warranted. Indeed, in the current study the reward association had no effect on actual behavioral choice, as the stimulus-response association was the same for both rewarded and unrewarded events and subjects were not required to actually decide for a stimulus based on its expected valence. Nevertheless, the consequences of correct and fast responding to a stimulus with a reward association and one without such an association had different valences. While the normal task cues led to a neutral outcome, the reward cues offered the chance to acquire a fairly high reward for good performance. This allows for the inference that the left medial orbitofrontal activation in the present study most probably represented the positive feelings elicited by the reward association.

3.3.4 A proposed model of orbitofrontal function beyond the context of reward

Against the background of the above-discussed findings, the current results may fit well into a more general framework that is not restricted to the context of reward, but is extended to a wider range of motivationally significant stimuli in the environment. The proposed model of orbitofrontal function may apply for all salient stimuli that are of particular importance to the organism and represent motivational/ behavioral goals, regardless of whether they address subjective internal needs (like primary rewards) or whether they represent "cognitive incentives" created in the constrained context of the laboratory. A necessary prerequisite thereby also seems to be the salience of environmental stimuli next to their motivational significance, which also conforms to the results from the prior study from my laboratory (Gruber et al., 2006, in prep.).
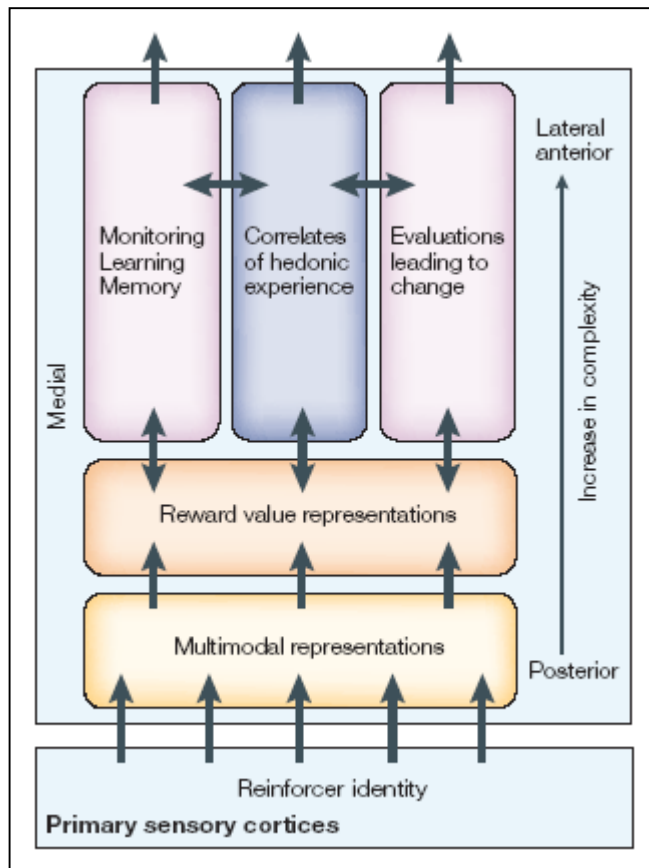
Figure 17: A heuristic model of orbitofrontal function (Fig. 17 was taken from Kringelbach, 2005).

Within this model of orbitofrontal function rather **medial parts of the (right) posterior OFC** (like the posterior olfactory sulcus and adjacent posterior orbital gyrus) may be assumed to represent all kinds of motivationally significant events in the environment, regardless of their actual valence. This process may thereby be modulated by either external inputs (e.g., an <u>unexpected</u> violation of a reward- expectation in reversal-learning paradigms), internal changes (e.g.,

changes in satiety state in reinforcer devaluation) or maybe even by both external and internal conditions. In that sense, medial posterior OFC seems to represent the "wanting" or "incentive salience" component of environmental events (cf., Berridge & Robinson, 2003) and subserves an evaluative function that allows for the subjective decision that a motivationally significant event is present. Furthermore, the individual consequences following motivationally significant events (i.e., the behavioral change and/ or hedonic feelings following these events) are presumably represented separately within the OFC. Against the background of the current findings, it may be assumed that coactivations observed in more **lateral parts** of both the **posterior OFC** and adjacent **frontoopercular cortices** as well as in **right anterior OFC** may thus not only be involved in the assignment of behavioral significance to salient stimuli in the environment, but instead further allow for voluntary goal-directed adjustments of behavioral control processes in order to achieve behavioral success and to avoid failure in situations that require a high degree of cognitive control. Finally, the **left medial orbital gyrus** might instead represent the positive hedonic feelings elicited by rewarded events and thereby

supposedly represents the "liking" component of reward (Berridge & Robinson, 2003).

A more fine-grained representation of different functions both along the posterior-anterior and the medial-lateral axes of the OFC, as indicated by the current results, would also be in accordance with the heuristic model recently proposed by Kringelbach (2004, 2005). According to Kringelbach (2004, 2005), after the assignment of relative reward value – or more generally speaking the assignment of motivational significance, as I would infer from the present observations – in relatively **caudal parts of the OFC**, the information is either relayed to **lateral OFC** to influence subsequent behavior (e.g., for reversing previous stimulus choice), to **more medial orbitofrontal regions**, similar to the ones found in the current study in association with reward, were it is made available for subjective hedonic experience, or to **orbitofrontal parts located near the brain's midline** (i.e., the gyrus rectus), that is assumed to subserve a monitoring function as important part of learning and memory mechanisms (see also: Fig. 17, p. 94). Still, based on the present results such a tripartite dissociation along the medial-lateral axis cannot be directly supported. Further, the current study was unable to unequivocally support the selectivity of most orbitofrontal activations (cf., pp. 69). For that reason, future studies need to carefully test the heuristic model proposed by Kringelbach (2004, 2005; see also: Future Directions, pp. 109).

3.4. Activations beyond the orbitofrontal cortex

It is important to note, that the orbitofrontal cortex does not function in isolation, but functionally interacts with other regions in the human brain. In the following sections of the discussion the remaining findings from the fMRI-experiment will be discussed with regard to their role within the framework of the current study. Reward thereby preferentially activated regions of the brain's reward circuit, while behavioral relevance of infrequency further led to responses in regions of the "adaptive reflexive processing network" (Kiehl et al., 2005a). Nevertheless, there were also regions that were activated in a similar way by both behavioral relevance of infrequency and reward, which may be interpreted as supposedly underlying the general processing of sensory properties of stimuli that are both salient and motivationally significant.

3.4.1 Similar activations for reward and behavioral-relevance of infrequency – Beyond the orbitofrontal cortex

Similar activations for different forms of biologically significant events outside of the OFC were basically restricted to the postcentral cortices and the inferior occipital cortex. Further, there was also an activation located in the left cerebellum, which occurred in association with both behaviorally relevant oddballs without and irrelevant oddballs with a reward association. These findings may be best interpreted as representing a general attentional mechanism, in the sense of an enhancement of both visual and somatosensory processing when subjects had to deal with salient motivationally significant events. In addition, I also detected similar activations in the amygdalae for both behaviorally relevant oddballs and events with a reward association, whereby in the right hemisphere activations associated with reward were located more posteriorly extending into the hippocampus-amygdala complex (cf., Table 3, p. 64). Overall, this observation strongly argued for a more general function of the amygdala in processing of motivational significance.

Somatosensory activity in **postcentral cortex** has commonly been observed in relation to movement execution, especially in situations that required a high degree of attentional and executive control (e.g., Lacourse et al., 2005). This was for instance the case when subjects had to execute a novel sequence of movements when compared to a skilled movement (Lacourse et al., 2005). A minority of reward studies also reported somatosensory activity (Berns et al., 2001; Elliott et al., 2003; Zink et al., 2004). In a study in which subjects had to swallow small amounts of liquid rewards, somatosensory activity was higher for a preferred reward when compared to a less preferred liquid (Berns et al., 2001). In the target-detection study of Elliott et al. (2003) a left postcentral response, similar to the one observed in the current study, was also found in association with reward that occurred contingent on a button press. And Zink et al. (2004) further observed a comparable left postcentral activation when monetary reward was received contingent on performance, but also when an arbitrary stimulus followed a correct button press. For that reason, I would interpret the postcentral activations, that occurred in association with both rewarded events and relevant oddball trials, as a sort of control signal in the sense of an on-line somatosensory feedback, that reassured subjects of whether a correct button press

actually took place. This would also explain, why the activations for both the irrelevant oddballs with a reward association and the relevant oddballs without such an association were more extensive than the ones for shape congruency with a reward association. While shape congruency simply required subjects to execute well practiced frequent standard responses, the relevant oddball trials necessitated an infrequent and therefore less well established response, which required a higher executive control effort than that to frequent events. Similarly, in trials with irrelevant oddballs that had a reward association it was particularly important to increase executive control processes in order to respond correctly and not to become distracted by the infrequent deviant.

Comparable to the postcentral cortex, the **cerebellum** has also been reported to play a central role in organizing sensory inputs and has further been found to be involved in planning or assigning motor responses to rewarding stimuli or other salient incentives. Accordingly, the cerebellum supposedly plays a fundamental role in a number of cognitive processes required for executing goal-directed behavior and suppressing disadvantageous behaviors (Anderson et al., 2006). In the current study, a part of this brain structure was consistently activated by both behaviorally relevant oddballs without a reward association and irrelevant infrequent events that were associated with the chance to gain a reward (cf., Table 3, pp. 64), but not by congruent shape trials associated with a reward. Due to their infrequency the former two events were especially salient. One might therefore assume that the cerebellar response was restricted to motivationally or behaviorally relevant events that were also perceived as particularly salient, because different from congruent shape trials these events appeared unexpected in the shape task and therefore required a high degree of cognitive control to ensure successful performance (i.e., achieve either the adjustment of behavior towards the relevant oddballs or ignoring of the irrelevant oddballs with a reward association). If one further considers the observation that the cerebellum gets direct input from the midbrain dopamine system (e.g., the VTA, Ikai et al., 1992), which has also been shown to be important for the processing of all sorts of salient stimuli and incentives, one could therefore presume that the cerebellum should be especially responsive to salient events in the environment.

Activations in **inferior occipital cortex and gyrus fusiformis**, that were similar for different forms of behaviorally relevant events (cf., Table 3, pp. 64), indicated that visual processing was also enhanced in situations that required a high degree of executive control. Attention has already been observed to modulate activation in extrastriate sensory regions (Yantis & Serences, 2003; Thiel et al., 2004) or other parts of the ventral visual stream (Gazzaley et al., 2005), which has been assumed to be mainly guided by top-down signals from higher processing regions like the prefrontal and parietal cortices (Yantis & Serences, 2003). Attentional modulation of extrastriate activity may be therefore viewed as a top–down bias, which facilitates processing of stimuli at attended locations (Thiel et al., 2004). In the current study, rewarded events and the behaviorally relevant events constituted motivational goals and were both represented by a similar region in right posterior orbitofrontal cortex, while similar parietal activations, except from those found in postcentral cortex, could not be detected. Whether this orbitofrontal subregion indeed provided the top-down bias that enhanced visual processing of motivationally relevant stimuli has to be assessed in future studies. Still, there is already evidence that a greater activation in early extrastriate and ventral temporal areas for emotional relative to neutral visual stimuli (e.g., faces) could result from direct feedback influences exerted on perceptual pathways by other regions involved in emotional processing (for example by the amygdala, e.g., Vuilleumier et al., 2004).

And indeed, I also observed activations in the **amygdalae** that occurred unselective for all types of motivationally or behaviorally relevant stimuli in the present study, which may indicate that the amygdala also underlies a general function in the processing of motivational significance which could be even similar to the one of the posterior OFC. The amygdala has been observed to be sensitive to positive emotions (Ernst et al., 2005), perceived reward value (Gottfried et al., 2003), positive valent stimuli (e.g., O'Doherty et al., 2003; Elliott et al., 2004) and stimuli with a high incentive motivation (e.g., Arana et al., 2003). Still, this region has also been implicated in the acquisition and expression of fear responses (e.g., Morris & Dolan, 2004; see also: Whalen, 1998; Calder et al., 2001) and has been assigned an important role as an automatic "alarm center" for innate threat cues (Williams, 2006). In particular, the right amygdala has thereby been assumed to be a key component of the "Fight/ Flight system" (cf., Williams, 2006). Moreover, some

recent studies further directly supported, that the amygdala indeed showed a valence-independent response to all stimuli that were of high emotional salience (Garavan et al., 2001; Liberzon et al., 2003; Phan et al., 2004; Lewis et al., 2006). Similar to the OFC, the amygdala may even be considered as a general „relevance detector" devoted to the processing of a broader category of biologically significant stimuli independent from their actual affective valence (cf., Sander et al., 2003). In addition, there is evidence for an interaction between the phylogenetically older amygdala and the orbitofrontal cortex in processing of motivational relevance (e.g., in reinforcer devaluation studies). For instance, Izquierdo et al. (2004) reported observations from lesion studies with rhesus monkeys, which indicated that in situations in which responses were mainly guided by a motivational signal like the decreasing reward (or hedonic) value, the amygdala was supposedly one source that supplied information on the current motivational value of reinforcer that was important for behavioral choice. Similarly, an fMRI reinforcer devaluation study that manipulated the satiety status of human participants observed a significant decrease in the amygdala response upon increasing satiety, that paralleled activations in the posterior OFC (Gottfried et al., 2003). For these reasons, in the present study it seems to be likely that the amygdala could have somehow interacted with the posterior OFC when encoding significant information that may be used to guide goal-directed behavior (see also: Schoenbaum et al., 1998). Nevertheless, in the previous study of Gruber et al. (2006, in prep.) activations in the amygdalae did not show up when assessing the interaction of behavioral relevance and infrequency (see also: Table 4, p. 79), which may further indicate, that different from the (lateral) posterior OFC, the phylogenetically older amygdala apparently was not vital for the rapid adjustment of goal-directed behavior towards unexpected infrequent deviants (i.e., the relevant oddballs).

3.4.2 Activations selective for rewarded events - Beyond the orbitofrontal cortex

Even though the direct contrasts did not provide unequivocal evidence that most of the below discussed regions were indeed selective for reward (cf., pp. 69), it is most likely that these brain regions were preferentially involved in reward processing in the current study. It has already been outlined in the introduction (pp. 12) that

processing of positive incentives has not been exclusively observed in the OFC. Among them were the right nucleus accumbens, which was activated by irrelevant oddballs with a reward association, and various parts of the occipital and temporal cortices as well as the left hippocampus that responded to all events with a reward association. In the present study, these regions supposedly subserved complementary functions like the contextual integration of reward-related information or the representation of the increased salience of events with a reward association.

One "classical" reward-sensitive region, that was however only inconsistently associated with reward in the present study, was the right **nucleus accumbens**. The nucleus accumbens has been shown to represent reward anticipation (Knutson et al., 2003; Galvan et al., 2005), general processing of reward (Kirsch et al., 2003) and positively valenced emotional stimuli (Aharon et al., 2001). In the present study it was exclusively activated by irrelevant oddballs with a reward association, but not when a congruent shape stimulus was associated with a reward. Considering the observation made by Zink et al. (2003), a response in nucleus accumbens should most likely occur in situations of high salience regardless of their hedonic value and the behavioral response requirements associated with the salient event. Nevertheless, such an assumption would have also applied for situations in which subjects encountered any kind of salient oddball event in the present study, which was however not the case. One might therefore speculate that in the present study one possible explanation for an activation of the nucleus accumbens, that exclusively occurred when an irrelevant oddball was also associated with a reward, may be derived from its function as a "critic" that learns to predict future rewards based on the reward-prediction error (O'Doherty et al., 2004) and the interplay of two contrary processes. First of all, subjects were required to ignore the oddball stimulus and to voluntarily redirect attention towards the relevant stimulus attribute shape. This could have represented a classical withdrawal or avoidance situation. On the other hand, the irrelevant oddball (or the classical withdrawal situation) was on some occasions nevertheless associated with a reward. So it might have been the reward association within an infrequent withdrawal situation, that could have been perceived as a kind of reward prediction error, which then led to the activation of nucleus accumbens. Alternatively, apart from the first speculation which remains to be directly assessed by future studies, the activation in nucleus accumbens in that

particular situation could have also been an overall effect of the increased salience of an irrelevant oddball event that was further presented in the context of a reward association that may have also entailed an increased salience. However, this latter explanation is also *post hoc* and therefore remains to be directly tested.

In addition, reward also partly selectively activated the **extrastriate cortex** and **multi-modal association cortices** in the temporal lobe. Similar activations were also found in some prior reward studies (e.g., Elliott et al., 2003), but were not further interpreted by the respective researchers. One might again assume that the reward association itself increased visual salience of the respective target events, since in the present study the task cues provided the actual reward information, while both target-stimuli with and without a reward association never differed with regard to their visual properties.

Finally, rewarded events further selectively activated the left hippocampus. Even though the **hippocampus** is no classical structure of the brain's reward circuit, but has rather been assigned an important role in memory processes (e.g., declarative memory; cf., Cohen et al., 1999), it was still activated by rewarded stimuli in the current study. Only a minority of studies on reward processing observed hippocampus activation in association with positive reinforcers as well as punishment (O'Doherty et al., 2002; Elliott et al., 2000a; Small et al., 2001) and for that reason a coherent explanation for its involvement in the processing of reward is still missing. Nevertheless, one line of evidence points to an interaction between the hippocampus and other regions involved in processing of emotional stimuli. For instance, the hippocampus and the amygdala have been consistently observed to interact in the consolidation and enhancement of memory for emotionally laden information (cf., LaBar & Cabeza, 2006). Lesion studies with human subjects led to the assumption that the amygdala may represent implicit emotional learning processes (e.g., fear conditioning), whereas intact hippocampus functioning is presumably vital for conscious factual representations of stimulus-reinforcement contingencies (Bechara et al., 1995) and for contextual representations (LaBar & Phelbs, 2005). A similar relationship has also been observed in memory retrieval, which was expressed by an enhanced effective connectivity between hippocampus and amygdala when retrieving emotional memories (Smith et al., 2006). Even

though, the present study included not explicit memory component, subjects nevertheless had to remember the meaning of the reward cue. It is therefore probable, that in accordance with the proposal made by Smith et al. (2006) in the present study the amygdala processed emotional information concerning the reward association, which was supposedly retrieved from hippocampus-dependent memory.

3.4.3 Processing of irrelevant and behaviorally relevant infrequency – Beyond the orbitofrontal cortex

The observed oddball-activations largely corresponded to those that had been previously detected in the common oddball paradigm, when humans either processed infrequent target or distractor stimuli (e.g., Bledowski et al., 2004) or were required to respond to unexpected (infrequent) changes in different modalities (e.g., Downar et al., 2000, 2001). Brain regions activated by irrelevant oddball stimuli in the present study (cf., Table 1, p. 59) comprised right superior and medial frontal as well as bilateral middle frontal areas. In addition, activation foci within intraparietal cortices on both sides were detected and the irrelevant oddballs also activated extrastriate cortex and the right cerebellum. The presentation of behaviorally relevant infrequent events also activated a widespread and partly selective neural network of brain regions that included various frontal, parietal and temporal regions as well as occipital regions of the visual cortex, adjacent parts of the cerebellum and subcortical nuclei like the thalamus (cf., Table 2, pp. 61). In this section I will address common activations that were similarly detected for all infrequent events regardless of their behavioral relevance, while the next section will deal with those activations that were selective for behavioral relevance of infrequency.

A common attribute of both irrelevant and behaviorally relevant oddballs was their overall salience (i.e., their infrequency), which naturally suggested that activations caused by both oddball-types were in fact induced by stimulus-salience *per se*. Nevertheless, with reference to previous studies it was rather unlikely that all of the above mentioned regions simply represented the infrequency aspect that was inherent to all oddball events regardless of their behavioral relevance. Instead, different regions seemed to underlie specific roles like attentional reorienting (middle frontal

gyrus & intraparietal cortex), general motor preparedness (pre-SMA) and processing of visual salience (occipital cortex), which will be addressed in further detail below.

In the present study, activations within left middle frontal cortex were likewise detected for both irrelevant and for behaviorally relevant oddball events. This was in contrast to results from previous studies, which reported activations in **middle frontal gyrus** almost exclusively in association with behaviorally relevant infrequent events in common oddball studies (e.g., McCarthy et al., 1997; Kirino et al., 2000; Brázdil et al., 2005). Moreover, activity in this region was preferentially observed in tasks that either required subjects to overcome automatic or prepotent responses or to implement infrequent response rules or strategies that were stored in memory (Kirino et al., 2000; Huettel & McCarthy, 2004) or to spatially reorient attention following invalid spatial cues (Thiel et al., 2004). In sum, the middle frontal gyrus most likely represents a mechanism that identifies stimuli that require a response and that implements the initiation of a motor response (Kirino et al., 2000). With regard to the present results, one may assume that the relevant and the irrelevant oddballs activated middle frontal gyrus in a similar way, because both oddball events required a voluntary orientation to a response-relevant stimulus feature. In case of the relevant oddball the infrequent oddball feature required subjects to overcome a prepotent widely automatic response tendency to be able to execute the infrequent response, whereas the irrelevant oddball color, which involuntarily captured subjects' attention, nevertheless required subjects to voluntarily <u>redirect the attention</u> back to the relevant stimulus dimension shape and respond accordingly. Due to this prerequisite the response demands were different from those in common oddball paradigms, as in the present study subjects had to respond to every stimulus and also process bivalent stimuli of which the actually irrelevant stimulus-dimension elicited the orienting reflex. Conversely, in the classical oddball paradigm both univalent targets and distractors were commonly processed in the focus of attention and occurred in succession with frequent standard stimuli and, even more importantly, distractors required <u>no response initiation</u> in most of these studies. Alternatively, it is also possible that the activation in middle frontal gyrus occurred in association with both oddball conditions because subjects attributed the behavioral relevance aspect of one oddball type also to the other at least in some trials (this possibility has already been outlined for the posterior orbitofrontal activation, cf., pp. 82). Support for this assumption comes from the study of Downar et al. (2001), who also observed

activation within left middle frontal gyrus that occurred unspecifically for both task-relevant changes and irrelevant changes in the currently unattended modality. In their study deviants were presented concurrently in two different modalities and subjects had to attend to one of these modalities at a time, whereby, upon a cue change, the relevant modality switched every now and then. Each modality was therefore at least potentially relevant even when being currently irrelevant, which makes it possible that subjects in fact attended to both modalities and identified potentially relevant stimuli that led to activations in middle frontal gyrus, but only reported changes in the currently relevant modality.

With regard to activations detected in the **pre-SMA extending into the SMA** the absolute maxima observed for irrelevant oddballs and relevant oddballs lay in the right (x-coordinate = 3) and in the left hemisphere (x-coordinate = -3), respectively (cf., Table 1, p. 59, and Table 2, pp. 61). Nevertheless, the two clusters strongly overlapped and were not detected in the direct comparison between behaviorally relevant oddballs and irrelevant oddballs (cf., Table 3, pp. 64), which indicates that activations in these regions were probably unselective to oddball-type. And indeed, the **SMA** has commonly been reported to exhibit a rather unspecific activation that occurred in relation to both relevant and irrelevant low-frequency events in previous oddball studies (Downar et al., 2001; Mulert et al., 2004), which has been interpreted as the representation of involuntary motor orienting towards changing sensory input, even in situations in which the actual response remained unexecuted (Downar et al. 2000). In addition, the **pre-SMA**, in which the absolute local cluster maxima were located, has been assigned a complementary function in movement execution. Accordingly, the pre-SMA, which receives inputs from both the prefrontal cortex and the cingulate motor areas, has been assumed to be responsible for movement-related decision-making (Clare, 1997), particularly in situations in which the relevant responses are uncertain or ambiguous (Ullsperger & von Cramon, 2001; Garavan et al., 2003; Milham & Banich, 2005). It is therefore likely, that the pre-SMA was also engaged by a sudden, unexpected change in sensory input (i.e., the infrequent oddball colors in the present study), supposedly leading to a state of general preparedness that facilitated a change in behavioral strategy in ambiguous situations and possibly also supported actual movement execution in the present study.

Similar to the SMA, in previous oddball studies the **intraparietal cortex** has also been reported to respond in a context-insensitive fashion to both attended targets and unattended distractors (Marois et al., 2000; Downar et al., 2001; Bledowski et al., 2004). Furthermore, increased activations within intraparietal cortices, which were similar to the ones observed in the present study, were also observed in studies in which trials were invalidly cued and subjects were required to reorient attention in space in order to be able to respond correctly to a target stimulus (Nobre et al., 1999; Thiel et al., 2004). Thus, the unselective intraparietal activations observed in the present study may be best interpreted as representing the reorientation or disengagement of attention following the detection of unpredicted sensory events. The orienting reflex led to an involuntary disengagement of current attention that was centered on the shape task and required a subsequent <u>voluntary</u> (re)orientation of attention to the relevant stimulus dimension and the respective task set (i.e., in case of irrelevant oddballs this was a reorientation to the shape task set, while with regard to relevant oddballs an updating of the relevant-oddball task set was required).

Finally, activation foci detected within **right inferior occipital cortex and fusiform gyrus**, that occurred nonselective for both irrelevant and behaviorally relevant infrequency (cf., Table 1, p. 59; Table 2, pp. 61), may be most likely ascribed to the sensory distinctiveness (i.e., the salience) of the oddball colors yellow and white. According to theory, stimuli which strongly deviate from the neuronal model built from the repetitive features of the environment are perceived as particularly salient (cf., Sokolov, 1963). In the present study, the "visual" context was dominated by the standard colors red and blue, which were naturally perceived as less visually salient than the infrequent oddball colors. For that reason, the salience of oddball events was probably enhanced. Since the salience of stimuli that require a behavioral response has also been reported to often lead to stronger and more robust responses (cf., Sokolov, 1963), it was not surprising to further detect a quantitative activation-difference in the direct comparison between relevant and irrelevant oddballs with stronger activations when oddballs were also relevant for the behavioral response to be given (cf., Table 3, pp. 64),

3.4.4 Selective processing of behaviorally relevant infrequency – Beyond the orbitofrontal cortex

In contrast to irrelevant oddballs, processing of behaviorally relevant oddballs was preferentially associated with activations in regions of the "adaptive reflexive processing network", that have consistently been observed to exhibit enhanced activity in response to target stimuli (e.g., Bledowski et al., 2004; Kiehl et al., 2005a). Besides the already discussed activations in orbitofrontal cortex, relevant oddballs thereby selectively activated extensive parts of the temporal cortices bilaterally (e.g., the TPJ), the left insular cortex, parts of the parietal cortex and deep gray nuclei like superior colliculi and the thalamus (cf., Table 3, pp. 64).

Within the "target-detection network" especially the **TPJ** – and to a minor degree also the inferior frontal cortex – has been assigned a key role in identifying salient sensory events of (potential) relevance to behavior (Downar et al., 2001; see also: Corbetta & Shulman, 2002). The TPJ has been observed to be involved in processing of visual and auditory oddball-targets that either required silent counting or a button-press (e.g., Linden et al., 1999; Kiehl et al., 2001a, b) and for targets but not distractor oddballs in a study using the visual oddball paradigm (Clark et al., 2000). Interestingly, Downar et al. (2000, 2002) also found the TPJ to be responsive to the passive perception of unexpected changes (Downar et al., 2000) and to novel stimuli (Downar et al., 2002) in the visual, auditory and tactile modality. Nevertheless, the TPJ still showed a context-dependent enhancement when changes were task-relevant compared to irrelevant changes in most previous studies (e.g., Bledowski et al., 2004), and subregions within the TPJ (i.e., a part of the supramarginal gyrus) further exhibited a selective response for behaviorally relevant stimuli (Downar et al., 2001). In general, the TPJ may therefore be assigned the role of an important mediator of stimulus-driven attention in the sense of an alerting system that immediately directs attention towards salient (potentially) behaviorally relevant stimuli that are outside of the current focus of attention (cf., Corbetta & Shulman, 2002). The present results support this assumption, because the behaviorally relevant oddballs always appeared in the shape task and were therefore presented in the currently unattended stimulus-dimension. Further, trials with relevant oddball events required subjects to successfully detect the infrequent relevant stimulus-attribute color, that was

presented outside of the focus of attention, in order to be able to execute the correct response. The apparent selectivity for behavioral relevance of infrequency observed in the present study (cf., Table 3, pp. 64) thereby underlined that the TPJ was indeed particularly responsive to salient changes in the environment that required a rapid adjustment of goal-directed behavior, but not to salient events *per se*.

In the present study the processing of the response-relevant oddball stimuli of course was not strictly stimulus-driven, but also required the voluntary processing of the prospective memory targets that were behaviorally relevant (i.e., the relevant oddball stimuli). Considering an interplay between voluntary and strictly stimulus-driven processes in the brain, as proposed by Corbetta and Shulman (2002), it might be possible that the TPJ was indeed biased towards the relevant oddball color, due to an enhancement of the sensory salience of behaviorally relevant oddballs by top-down signals from frontal or parietal cortices (Corbetta & Shulman, 2002). Apart from temporoparietal activations, further activations within the ventral frontoparietal alerting network (cf., Corbetta and Shulman, 2002), were detected in the middle frontal gyri bilaterally, but in the present study the middle frontal gyrus exhibited a nonselective activation for both relevant and irrelevant oddball events for reasons that have already been outlined above. In addition, significant activity was also detected in parietal cortex (left precuneus), which in the present study occurred indeed selective for behavioral relevance of infrequency. Nevertheless, in previous oddball studies, the **precuneus** did not show such a selectivity, but was activated by both relevant and irrelevant stimulus changes (Downar et al., 2000, 2001; Stevens et al. 2005). It therefore remains to be directly tested whether activation in this region indeed represented a top-down signal that biased temporoparietal cortices towards relevant oddballs by coding the (voluntary) attentional shift between the object features "shape" and "color" (Nagahama et al., 1999) or whether it was for instance rather associated with the increased attentional task demands in a situation in which subjects had to overcome a prepotent response-tendency in trials with a relevant oddball, as it has been proposed by other researchers (Barber & Carter, 2005).

Activations within **insular cortex**, have mainly been observed during target detection in the classical oddball paradigm (e.g., Clark et al., 2000, 2001; Braver et al., 2001; Bledowski et al., 2004; Mulert et al., 2004), even though some authors also

reported insular activation in response to novel and infrequent distractor stimuli that required no button press (Downar et al., 2001; Kiehl et al., 2005a). The functional role of this region within the "adaptive reflexive processing network" is still under discussion (Kiehl et al., 2005a) and for that reason the inference made by Bledowski et al. (2004), that at least the anterior insula – together with the frontoopercular cortex (see above) – may subserve a kind of retrieval function, still remains rather speculative. Nevertheless, the activation cluster detected in the present study was located deep in the middle insular cortex and was therefore clearly dissociated from the activation in frontoopercular cortex. Alternatively one may therefore hypothesize, that in the present study the insula could have represented the somatosensory recognition of the infrequently pressed response button, which was based on tactile information relayed by the somatosensory cortex (Burton & Sinclair, 2000), or could have contributed to the reassurance that the less automatic response to the relevant oddball stimulus had indeed been successfully executed. However, further studies are definitely needed to ascertain insula function within the context of behavioral relevance and infrequency.

As a region that gates both cortical input (i.e., what the cortex will see, hear and smell) and output (i.e., cortical "decisions" that allow us to run, speak, eat., cf., Trepel, 2004), the **thalamus** has been consistently found to be involved in the processing of relevant oddballs in both the visual and auditory modality (Clark et al., 2000; Downar et al., 2001; Kiehl et al., 2001a, b; Brázdil et al., 2005; Kiehl et al., 2005a). Since the thalamus was also selectively activated by the relevant oddball stimuli in the present study, it is most likely, that it was somehow involved in the motor response to these events, as assumed by other researchers (e.g., Downar et al., 2001).

Next to the thalamus, I also detected significant activations in the **superior colliculi**, that had already been found in the previous study by Gruber et al. (2006, in prep.). Even though activations in these considerably small nuclei have not been reported in previous fMRI oddball studies in humans, the superior colliculi have nevertheless been assigned an important role in the processing of visual salience in the rat brain (Comoli et al., 2003). Accordingly, short latency visual information has been observed to be relayed from the superior colliculi to the substantia nigra, which has

been assumed to represent the critical perceptual discriminations that identify stimuli as both unpredicted and biologically salient (Comoli et al., 2003). Still, a significant activation within the substantia nigra was lacking in the present study and one therefore has to be careful not to overinterpret activations detected in such small regions as the superior colliculi especially because in the present study a considerably high spatial smoothing factor was applied, which could have affected the exact localization of the respective maxima. Nevertheless, apart from the rather putative activations detected in the superior colliculi, the current study provided further support for an increased visual salience of the behaviorally relevant oddball events (van Rullen et al., 2003). Accordingly, extensive parts of the **ventral visual stream** (i.e., bilaterally along the temporal association cortices) and also of the right temporal **limbic association cortex** were selectively activated by behavioral relevance of infrequency.

4. Future directions

Considering the present findings it became obvious that the restrictions entailed by experimental approaches in the laboratory could obscure an integrated view on brain functions, and only allows us to look at a fraction of the "whole story". The orbitofrontal cortex has been of major research interest for more than 40 years (cf., pubmed-search for the term "orbitofrontal"). Nevertheless, previous studies have mainly focused on the OFC in the context of reward processing, positive emotions and reward-related decision-making. The current study provided initial support for the assumption, that orbitofrontal function may comprise more than a mere representation of positive reinforcers and relative reward value. Beyond the context of reward, the posterior OFC may consequently be considered as a prime cortical region that both detects and evaluates motivationally significant and behaviorally relevant events in the environment and further provides the decisive signal that allows for a context-dependent adjustment of behavior. Still, the present results also pointed to a selective role of the left medial OFC in the representation of positive reward value. For that reason, it should be of future interest to further **disentangle the motivational "wanting" and the affective "liking" components of reward** (Berridge & Robinson, 2003) with regard to their representation within the OFC. The

current paradigm did not allow for the unequivocal inference that the hedonic value of reward was indeed represented by the left medial OFC as this inference was made *post hoc* and was not addressed by the initial hypotheses. In addition, it was not possible to find out whether subjects perceived experimental conditions with a reward association as more pleasant than those without. Future studies should carefully deal with this issue by systematically varying both the motivational significance and the perceived pleasantness or aversiveness of primary reinforcers within a single study.

Another interesting aspect, that could not be addressed with the presently employed method, was the actual **time-of-onset of activation in regions involved in the processing of significant events in the environment**. The present study revealed activations both in regions of the "adaptive reflexive processing network" (Kiehl et al., 2005a) and in the posterior OFC that occurred in association with behavioral relevance of infrequency. In contrast, events with a reward association did not activate the former regions, but only activated the posterior OFC and also the amygdalae to a similar degree. Instead, the reward association led to significant responses in the hippocampus and less consistently also in the nucleus accumbens. As has already been outlined in the introduction, general stimulus-salience (e.g., the unexpectedness of a stimulus) may initially be represented in a rather stimulus-driven fashion, before in a second step this information might be integrated by higher-order processing regions of the frontal lobe, which have been assumed to assign motivational significance. The method of fMRI does not allow for a temporal resolution in the milliseconds range and is therefore not capable to correctly measure the temporal continuum of salience processing and processing of behavioral relevance. Consequently, in the future both the temporal continuum (with ERP) and the neural correlates (with fMRI) of significance processing ranging from bottom-up salience to top-down goal-directed behavioral relevance remain to be investigated concurrently in a single study (see for example: Williams, 2006 for a heuristic model on the temporal continuum of significance processing) to get an idea about the time-course of activational onsets.

In addition, the **functional connectivity between mainly bottom-up and top-down driven mechanisms** of cognitive and behavioral control should also be of interest for future studies. Inspired by the proposal made by Izquierdo et al. (2004), who inferred that the guidance of goal-directed behavior represented by the OFC may depend on

different neural input sources depending on whether the most relevant information for current behavior comes from internally generated affective signals or external changes in visual stimulation, one may assume that regions that process visual salience should preferentially show a strong functional connectivity with orbitofrontal regions, whenever a <u>rapid</u> behavioral reversal has to be initiated upon a sudden (external) change in visual input regardless of the actual hedonic valence of the event that actually triggered this reversal (e.g., when subjects detected a relevant oddball color in the present study or when a negative feedback in reversal-learning studies required subjects to immediately reverse stimulus-choice). Conversely, in situations in which responding is guided by a more reliable affective signal (like the decrease of reward value in situations of increased satiety), the amygdala should show a strong connectivity with the OFC. A major question would thereby be, whether the functional connectivity would be restricted to the posterior orbitofrontal region that was similarly activated by both behavioral relevance of infrequency and the reward association in the present study, or whether posterior regions would rather be connected to activations that occurred in lateral posterior OFC (associated with the behavioral adjustment) and medial orbital gyrus (exclusively activated by positive events in the current study). Izquierdo et al.'s (2004) study did not sufficiently answer this question, because the ablation of the monkey OFC had not been restricted to a part of the OFC, but had been applied to the whole region.

Apart from the temporal continuum and the functional connectivity, even more importantly, it should be of future interest to investigate, **how the orbitofrontal cortex is actually able to differentiate between aversive and positive stimuli and also neutral but nevertheless salient events that require a behavioral adjustment** (like in the present study), if all kinds of motivationally significant stimuli are initially represented by a similar posterior OFC-subregion. Taking into consideration the findings made by Ravel et al. (1999, 2003) who reported that tonically active cholinergic interneurons in the monkey <u>striatum</u> showed to be equally responsive to all kinds of motivationally significant events regardless of their actual valence, but nevertheless exhibited differential response patterns to either pleasant or aversive stimulation (e.g., a triphasic response for aversive stimuli), one may hypothesize that the same posterior orbitofrontal neurons could have also exhibited such a differential response pattern that might have differentiated between different types of motivationally significant stimuli (i.e., relevant oddballs and events with a reward

association) in the present study. Alternatively, it could have been also possible that some neurons within the same voxel responded preferentially to reward and others fired upon the detection of a relevant oddball that required a behavioral adjustment. The method of fMRI is not sensitive enough to detect subtle changes in a single neuron's firing rate as it measures the more extensive BOLD response and for that reason only single-electrode recordings in monkeys would provide evidence for such a process taking place in the posterior OFC.

Finally, the **link between deficient orbitofrontal function and the etiology of psychiatric disorders** remains to be further elucidated. Some psychiatric populations have already been reported to be unable to appropriately filter information with regard to their salience and/ or relevance within the current context in which they occur (e.g., oddball target processing in schizophrenics, Kiehl et al., 2005b) while others showed to be affectively biased in the processing of significant information in the environment (e.g., the mood-congruent bias observed in depressives, Elliott et al., 2002) or lacked the ability to overcome perseverative responses and adjust their behavior in a context-sensitive fashion (e.g., perseverative or compulsive behaviors observed in OCD-patients, cf., Zimmer, 2004). Not surprisingly, these populations have also been reported to exhibit significant deficits in brain-function when compared to normal controls (for a review of recent neuroimaging findings on reward processing and decision-making in psychiatric patients see: Schlueter et al., 2006, accepted). The paradigm used in the present study would allow for a further elucidation of disorder-specific disturbances of "normal" orbitofrontal functioning in the context of significance processing, motivation and affect. There is already evidence, that for instance substance abusers lack the ability to make adaptive decisions when it comes to the selection of natural rewards. At the same time, these patients have been reported to exhibit an aberrant orbitofrontal activation pattern in response to motivationally significant stimuli (cf., Schoenbaum et al., 2006), which has been interpreted in terms of a reduced valuation of natural rewards by the OFC which is also evident in a general hyperresponsiveness to stimuli predicting drug-availability enhancing glutamatergic drive to these predictors (cf., Kalivas & Volkow, 2005). It should be fruitful to test these as well as other psychiatric patients with deficits in motivational processing and decision-making with the currently used paradigm since this paradigm has the decisive advantage that it does not present disorder-related or symptom-provoking stimuli (e.g., pictures of

drug stimuli or pictures related to compulsions) and may therefore be easily applied to a broader range of psychiatric patients.

5. Critical remarks

This section provides the interested reader with some final and somewhat critical remarks on the present study. It is intended to support upcoming research on motivational significance by pointing to some (methodological) shortcomings that should be avoided in the future.

For reasons that have been outlined above, I cannot unequivocally infer that lateral posterior OFC and also its right anterior parts were selectively activated by behavioral relevance of infrequency, because these activations did not show up in the direct subtraction contrasts between behavioral relevance of infrequency and events with a reward association (cf., pp. 69). However, the **overall low statistical power** of the current study supposedly was one reason for this insensitivity for selective OFC activations related to different behaviorally relevant events. In order to increase statistical power, future studies therefore should for instance increase the **temporal resolution** by introducing a systematic variation of trial onset (i.e., jittering; Miezin et al., 2000). In addition, it would have also been desirable to test **a bigger sample of healthy participants**. Even though 10 subjects sufficed for a random-effects analysis and led to reliable results across the group in the present study, a number of 20 subjects or more could have further increased reliability and would have probably also affected statistical power. Moreover, a bigger sample would have also provided the opportunity to test for **potential gender differences**. There is already evidence for a sexual dimorphism in the orbitofrontal response with respect to biologically significant stimuli in the environment (e.g., threats, McClure et al., 2004b) and it remains to be tested whether such a difference also affected processing of motivationally significant events like the ones used in the present study. However, the limited time-frame for data acquisition of the present study did not allow for assessing more than 12 individuals.

VII. Appendix

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2. List of abbreviations

ANOVA	analysis of variance
BIC	brain imaging center
BOLD	blood oxygen level dependent
CI	competitiveness index
CRs	correct responses
EPI	echo-planar image
ER	event-related
fMRI	functional magnetic resonance imaging
FWE-correction	family-wise-error correction
FWHM	full-width half-maximum
GLM	general linear model
GRF	gaussian random fields
^{1}H	hydrogen
MNI	Montreal Neurological Institute
NC	neurological convention
OFC	orbitofrontal cortex
PC	personal computer
PET	positron emission tomography
pre-SMA	pre-supplementary motor area
RC	radiological convention
RTs	reaction times
SD	standard deviation
SMA	supplementary motor area
SPM2	statistical parametric mapping
T1	longitudinal relaxation time
T2	component of the transversal relaxation time (p. 31)
T2*	component of the transversal relaxation time (p. 31)
TCI	temperament and character inventory
TPJ	temporoparietal junction

voxel   volume element

VTA   ventral tegmental area

3. List of figures

4. List of tables

5. Publications

5.1   Research articles

[1]   Gruber O, Karch S, **Schlueter EK**, Falkai P, Goschke T (**2006**) Neural mechanisms of advance preparation in task switching. Neuroimage 31: 887-895

[2]   Gruber O, **Schlueter EK**, Kirchenbauer L (*2006, in preparation*) Modulation of regional brain activations through the behavioral relevance of low-frequency events.

[3]   **Schlueter EK**, Gruber O (*2006, in preparation*) Dissociating the neural correlates of different types of biological significance.

5.2   Reviews

[1]   **Schlueter EK**, Gruber O, Falkai P (*2006, accepted*) Neural correlates of cognitive deficits in psychiatric disorders: Reward processing and decision-making. Psychosocial Medicine

[2]   Gruber O, **Schlueter EK**, Falkai P (*2006, submitted for publication*) Die funktionelle Organisation des frontalen Kortex: II. Ihre Relevanz für psychiatrische Störungsbilder. Fortschritte der Neurologie · Psychiatrie.

[3]   **Schlueter EK**, Gruber O (*2006, submitted for publication*) Die funktionelle Organisation des frontalen Kortex: I. Grundlegende Erkenntnisse aus den Systemischen Neurowissenschaften. Fortschritte der Neurologie · Psychiatrie

5.3   Published abstracts

[1]   **Schlüter E**, Christiansen K, Knuth, UA (**2003**) Stress und Infertilität des Mannes: Eine empirische Studie. In: Greil H, Scheffler C (Hrsg.) Anthropologie der Geschlechter. Universitätsverlag Potsdam: Potsdam, p. 120

[2]   Gruber O, Rosenblum K, Melcher T, Gruber E, **Schlüter EK**, Scherk H, Pajonk FG, Falkai P (**2005**) Experimental neuropsychological testing of attentional and executive functions in the evaluation of pharmacological treatment responses to methylphenidate in patients with adult ADHD. Pharmacopsychiatry 38: 245

[3]   **Schlueter EK**, Kirchenbauer L, Melcher T, Gruber O (**2005**) Modulation of regional brain activations through the behavioral relevance of low-frequency events. Neuroimage 26, Suppl. 1: S53

[4]   **Schlueter EK**, Gruber O (**2006**) Dissociating the neural correlates of different types of biological significance. Neuroimage 31, Suppl. 1: S156

5.4   Talks and poster presentations

[1]   **Schlüter E**, Christiansen K, Knuth, UA (**2003**) Stress und Infertilität des Mannes: Eine empirische Studie. *Talk at the 5th congress of the „Gesellschaft für Anthropologie" in Potsdam/Germany*

[2]   **Schlueter EK**, Kirchenbauer L, Melcher T, Gruber O (**2005**) Modulation of regional brain activations through the behavioral relevance of low-frequency events. *Posterpresentation at the 11th conference of the Organization for Human Brain Mapping in Toronto/Canada*

[3]   **Schlueter EK**, Gruber O (**2006**) Dissociating the neural correlates of different types of biological significance. *Posterpresentation at the 11th conference of the Organization for Human Brain Mapping in Florence/Italy*

6. Acknowledgements (Danksagung)

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