Good vibrations: Rhythms and plasticity in neural correlates of value in rat orbitofrontal cortex

van Wingerden, E.J.M.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
CHAPTER 1

GENERAL INTRODUCTION

“The primary purpose of the brain is to produce future”
Daniel Dennett, Consciousness Explained (1991)
Chapter 1. GENERAL INTRODUCTION

The functions of the orbitofrontal cortex, or OFC for short, have been a matter of debate over the years. Arguably, one can have a near-to-normal life without any orbitofrontal cortex whatsoever. The neuropsychological examination of patients with damage to the orbitofrontal cortex (by stroke, traffic accidents or, in one case, an iron rod passing through the frontal cortex) usually reveals no differences in IQ, language and motor skills or memory performance compared to uninjured people (e.g. Harlow, 1868; Damasio et al., 1994; Rolls et al., 1994; Beer et al., 2006). In fact, at one period in time, the practice of destroying large parts of the prefrontal cortex called lobotomy that targeted predominantly the ventromedial aspects that include the orbitofrontal cortex, was deemed an appropriate treatment for patients suffering from psychiatric illnesses (Freeman and Watts, 1937; Lerner, 2005). As reported by Freeman, damage to the orbitofrontal cortex often induces changes in the personality and social behavior of patients. Freeman maintained for many years that these changes were, on the whole, for the better. However, we now recognize that these personality changes in itself are detrimental: it is not uncommon for patients with orbitofrontal damage to become alienated from colleagues, friends and loved ones. Close relatives characterize the social behavior of these patients as childish (epitomized by the tendency to tell poor jokes, known as Witzelsücht, Mendez, 2005), self-centered with little concern for other peoples’ feelings, inappropriate or rude and short-sighted (Eslinger and Damasio, 1985; Meyers et al., 1992; Rolls et al., 1994; Beer et al., 2003). Amazingly, these patients seem to be entirely unaware of their social faux-pas as they are making them, but retain the ability to detect their own aberrant behavior (Beer et al., 2003, 2006). Next to errors in the social domain, orbitofrontal patients make poor long-term, financial decisions exacerbating their problems in readjusting to society. How can these diverse problems and symptoms stem from damage to a single area of the brain? We can conceptualize the orbitofrontal syndrome as an overarching deficit in (social and non-social) decision making that hinders patients in creating appropriate forward models or expectations of the possible consequences of their actions, whether these are financial decisions or bluntly honest comments on a person’s appearance. In the following paragraphs, I will first describe the anatomical connections of the OFC and next introduce the invasive and noninvasive studies of OFC activity to outline the type of information processing that could be performed by the orbitofrontal cortex.
The studies that I have performed have mainly focused on the temporal dynamics of orbitofrontal activity. Temporal pattering of neuronal activity is thought to be crucial for cross-structural communication in the brain, and I will therefore conclude this general introduction with a focused review of the involvement of rhythmic neural activity in cognition, and how this could apply to the proposed network function of the OFC.

**Neuraneatomy of the orbitofrontal cortex**

Evolutionary homologous areas corresponding to the orbitofrontal cortex can be found in a wide range of species, such as rodents, cats and primates. Indeed, neuroanatomists have parcellated the ventral parts of the frontal cortex in humans, macaques (a genus of Old World Monkeys) and rats in different subregions based on cytoarchitectonic characteristics, pointing out similarities in general organization (Brodmann, 1909; Walker, 1940; Carmichael and Price, 1994; Groenewegen and Uylings, 2000; Öngür and Price, 2000). However, notwithstanding these similarities, there are notable differences between the orbitofrontal cortices of primates, including humans, and other mammals. With the expansion of frontal cortex, granulated 6-layered cortex - marked by a distinct layer IV containing neurons with small, granulated cell bodies - has evolved in the more anterior aspects of the frontal cortex in primates, in contrast to the agranular nature (lacking a clearly identifiable layer IV) of these brain structures in rodents (Fig. 1.1, from Wallis, 2012). This has prompted some researchers to state that we cannot readily draw functional comparisons between primate orbitofrontal cortex as a whole and the rodent homologue (e.g. Preuss, 1995; Wise, 2008; Rudebeck and Murray, 2011). At the same time, some of these authors and others do stress that the rodent orbitofrontal cortex shows remarkable anatomical and functional homology to the agranular parts of the primate orbitofrontal cortex, however, allowing careful cross-species comparisons (Uylings et al., 2003; Wise, 2008; Wallis, 2012). Evidence for these homologies is at least threefold and stems from 1) similarities in the anatomical orientation, incoming or *afferent* connections and outgoing or *efferent* connections of agranular OFC in rats and primates; 2) similarities in intra-OFC connectivity patterns and 3) similarities in functional activity patterns in (social) decision-making situations. I will defer the functional comparison between rodent and primate OFC to a later paragraph and first discuss the evolutionarily
Chapter 1. GENERAL INTRODUCTION

preserved OFC connectivity patterns.

OFC: anatomical location
In both rats and primates (Fig. 1.1), the orbitofrontal cortex occupies the ventral surface of the rostral pole of the prefrontal cortex. Öngür and Price (2000) were the first to compare what they called the ‘orbitomedial prefrontal cortex’ or OMPFC among rats and primates, delineating an orbital and medial network based on the cytoarchitectonic and input/output criteria. Along a medial-to-lateral axis on the ventral orbital surface, further subfields of the OMPFC can be recognized: In rats, they are called the medial (MO), ventral (VO), ventrolateral (VLO), lateral (LO) and dorsolateral (DLO) orbitofrontal cortex (Fig. 1.1a; Palomero-Gallagher and Zilles, 2004). Caudally, these lateral structures border the agranular insular cortex (AI). In macaques, the caudal, agranular parts of the orbitofrontal subdivisions extend medially from area 14 on the gyrus rectus, via areas 11/13 between the medial and orbital sulci, also called central OFC, to the lateral area 12 and rostral parts of the insula (Fig. 1.1b, Carmichael and Price, 1994), with human subdivisions following basically the same nomenclature (Fig. 1.1c, Öngür et al., 2003). Medially, the OFC in rodents and primates borders the infralimbic and prelimbic (IL/PL) cortices that, together with anterior cingulate regions, make up the medial prefrontal cortex (mPFC, Fig. 1.1 top row).

OFC: connectivity patterns
If we are to draw functional comparisons on the role of the OFC in behavior between species, one of the underlying assumptions is that the parts of cortex that are included in such a functional comparison have access to the same general class of information (incoming projections) and have similar behavioral control options (outgoing projections). Öngür and Price (2000) identified orbital and medial networks within the OMPFC of rats and primates, defined by strong reciprocal cortico-cortical connections (Fig. 1.2; Öngür and Price, 2000; Wallis, 2012b). Importantly, these functional (as defined by connectivity patterns) orbital and medial networks do not overlap entirely with the anatomically defined orbital and medial cortices: the orbital network consists of most of the central and lateral orbital areas, while the medial network encompasses areas on the medial wall, but also some areas on the ventromedial (gyrus rectus in primates) part of orbital cortex. Some areas
Fig. 1.1 Comparative Anatomy of the Orbitofrontal Cortex

(A) Architectonic maps of the medial (top) and lateral (bottom) frontal cortex in rats; the medial (top) and orbital (bottom) surfaces of the frontal lobe in monkeys (B) and humans (C). Agranular cortex lacks layer IV. Dysgranular cortex contains a rudimentary layer IV. Granular cortex has a well-developed layer IV. Layer IV neurons are described as granular because their cell bodies are small and round, and changes in this layer are clearly visible as one transitions from agranular to granular cortex. AC, anterior cingulate area; AON, anterior olfactory nucleus; c, caudal; cc, corpus callosum; Fr2, second frontal area; I, insula; i, inferior; Ia, agranular infralimbic cortex; IL, infralimbic cortex; l, lateral; LO, lateral orbital area; m, medial; M1, primary motor area; MO, medial orbital area; o, orbital; p, posterior; Par, parietal cortex; Pir, Piriform cortex; PL, prelimbic cortex; r, rostral; s, sulcal; v, ventral; VO, ventral orbital area. Numbers indicate cortical fields, except that after certain areas, such as Fr2 and AC1, they indicate subdivisions of cortical fields. Figure reproduced from Wallis (2012).
Chapter 1. GENERAL INTRODUCTION

Fig. 1.2 Orbital and medial prefrontal networks in macaques

In the macaque frontal cortex (shown in orbital [A] and medial [B] view), a medial (pink) and orbital (blue) network can be identified. Regions in these networks make preferential connections within their own network. Figure reproduced from Wallis (2012).

that are shared by both networks, most notably the ‘bridging’ areas MO and VO in rats and area 13 in macaques, situated in between the medial and orbital networks, could serve as an interface between these networks (Öngür and Price, 2000; Price, 2007; Hoover and Vertes, 2011).

The input/output connections of these networks also differ notably. The orbital network has reciprocal connections to (multi-)sensory areas for many modalities: strong olfactory inputs from the piriform cortex, strong gustatory input from primary taste cortex and from the insula, visual input from area TE in the inferior temporal cortex and somatosensory information directly from areas S1 and S2. In contrast, the cortico-cortical inputs to the medial network are far less sensory-specific: apart from polymodal areas in the superior temporal cortex, they include the cingulate and retrosplenial cortex, and the entorhinal and parahippocampal formations. Both networks are reciprocally connected to thalamic nuclei, most notably the mediodorsal (MD) nucleus.
However, within the MD, again a medio-to-lateral differentiation in projections can be observed, with medial MD connecting to the medial network, and more lateral MD areas connecting to the orbital network. These partially overlapping, but separable reciprocal connection patterns are followed up by differentiated output patterns of the medial and orbital networks to the basal ganglia: whereas the medial network (and also AI on the lateral wall) projects densely to ventral and medial striatum (Nucleus Accumbens, medial Caudate and ventral Pallidum), the orbital network has its majority of striatal targets in more central striatal zones, such as lateral Caudate and medial pallidum (Carmichael and Price, 1995a, 1995b; Cavada et al., 2000; Ferry et al., 2000; Öngür and Price, 2000; Schilman et al., 2008; Groenewegen and Uylings, 2010; Hoover and Vertes, 2011). In fact, a ventro-medial to dorsolateral gradient of prefronto-striatal projections can be observed, with separate, but partly overlapping terminal fields of ‘sensori-motor’ projections to more dorsolateral areas and ‘viscerolimbic’ projections to ventromedial parts (Voorn et al., 2004; Groenewegen and Uylings, 2010; Pennartz et al., 2011b). The cortico-basal ganglia-thalamic loops are closed by the striato-pallido-thalamic connections, where are similar functional topography can be observed (Haber et al., 1995; Haber and Knutson, 2010).

Invasive and non-invasive studies of OFC function
A number of hypotheses on the function of the orbitofrontal cortex have historically been postulated. Apart from evidence indicating (social) decision making difficulties in patients with orbitofrontal damage described in early studies (Harlow, 1848, 1868), the first controlled assessments of behavioral changes following OFC lesions came from studies in cats and monkeys (Teitelbaum, 1964; Jones and Mishkin, 1972). These researchers found that animals with OFC lesions were especially impaired in changing their behavioral patterns when established rules or associations between stimuli and outcome were changed. A particular class of behavioral paradigms called *reversal learning* paradigms assesses the changes in performance and speed (measured as reaction time to salient events) of operant behavior in a controlled environment when rules governing the relation between stimuli and outcome(s) are changed (see Box 1, next page). Studies in humans, macaques and rats all indicate a pivotal role for the OFC in reversal learning (Rolls et al., 1994; Dias et al., 1996; Bechara et al., 1997; Bohn
Chapter 1. GENERAL INTRODUCTION

Box 1 Task Outline

In the studies presented in this thesis, rats were trained to associate one neutral stimulus (an odor cue A) with a positive outcome (a sweet sucrose solution) and a different stimulus (odor cue B) with a negative outcome (a bitter solution of quinine). Importantly, the rats had to perform an action (operant behavior) to obtain the outcome, and thus had the chance to avoid the negative outcome by not performing that action. In this Go/NoGo discrimination learning task, the experimenter tracks the choice behavior of the animal. Adopting naming conventions as used in signal detection theory (cf. Green and Swets, 1966), the responses can be classified as Hits, Misses, False Alarms & Correct Rejections (see Table 1.1). When the animal reaches a pre-determined proportion of correct responses (Hits + Correct Rejections vs. Misses + False Alarms, see table 1.1) well above performance at chance level, the rules linking stimuli and outcomes are reversed, so that the cue predicting positive outcome now is linked to a negative outcome. Now, the animals have to update the learned value of the outcome associated with the stimulus. The initial learning phase is usually referred to as the acquisition phase, followed by the reversal phase of the experiment. Actually, performance deficits based on failures to learn and failures to express the new contingencies (based on a failure to learn the new rules, or release the old rules) can become conflated in the reversal learning paradigm, as pointed out by Schoenbaum et al. (2011), but there exists a number of slightly different paradigms (for a comprehensive overview, see Dickinson, 1981) that make use of the technique of changing associative values to probe the contribution of neural systems to behavioral flexibility.

Table 1.1 Signal Detection Theory response conventions

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Response</th>
<th>Target Present</th>
<th>Target Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target Present</td>
<td>Hit</td>
<td>Miss</td>
<td></td>
</tr>
<tr>
<td>Target Absent</td>
<td>False Alarm</td>
<td>Correct Rejection</td>
<td></td>
</tr>
</tbody>
</table>
et al., 2003a; Chudasama and Robbins, 2003; Fellows and Farah, 2003; Schoenbaum et al., 2003a; Hornak et al., 2004; Izquierdo et al., 2004). Typically, in these studies, a lesion or inactivation of the OFC during the acquisition phase has no significant effect on the speed and accuracy of Pavlovian (stimulus-outcome) or instrumental (response-outcome) learning, indicating that other neural systems can support these types of learning. In reversal learning paradigms, new learning and suppression of learned associations are intertwined, complicating straightforward conclusions on the role of the OFC in these paradigms (see also Box 1). However, the role of the OFC during (initial) learning over and above reversal learning tasks becomes apparent in Pavlovian over-expectation tasks. In this task, several cues are independently associated with one and the same positive outcome. Next, in a compound training phase, they are presented together as cues, but the reward remains constant. Reinforcement learning theory (Rescorla and Wagner, 1972; Sutton and Barto, 1998) predicts that, while the overall outcome is still positive, this should present a slight disappointment to the well-trained rat: both cues still predict, with the same accuracy, a certain outcome. However, if the two cues activate separate representations of that outcome, the subject should expect double the outcome. In a sense, those two independent outcome representations are now both devalued, because their joint outcome turned out to be no more than each cue predicted by itself. Indeed, a reduction in conditioned responding to the cues, presented in isolation in a subsequent probe session, can usually be observed, in line with the idea that the expected outcome associated with the cue is now devalued compared to its previous level (e.g. Rescorla, 2006). However, if the OFC is unavailable during compound learning, this reduction in conditioned responding is absent (Takahashi et al., 2009). This suggests that the OFC plays a role in keeping track of which stimuli exactly are associated with, or to be credited for which level of reward, and in representing the (combined) expected outcome based on the current configuration of stimuli (Walton et al., 2010, 2011). In humans, the failure to integrate reward history (improper credit assignment) in decision-making is exemplified by the persistent disadvantageous choices made in the Iowa Gambling Task by patients with OFC/vmPFC lesions (Bechara et al., 1994, 1997).

The Iowa Gambling Task as a paradigm is widely used, though not uncontroversial. See for example Maia and McClelland (2004; 2005).
Chapter 1. GENERAL INTRODUCTION

Model-based or model-free representations of outcome?
This result highlights a discrepancy between electrophysiological studies into OFC activity conducted in rats on the one hand and similar studies involving non-human primates and noninvasive functional studies involving humans: the question whether the orbitofrontal cortex signals the value of outcomes predicted by stimuli or a particular course of action (model-free or cached representation), or the specific outcomes themselves (model-based representation). Value, in neuroeconomic terms, can be defined as an abstract variable that can move along a common currency scale, such that the value of 2 items of X is twice the value of 1X and so that higher value is more preferred than lower value and thus should lead to the choice of 2X over 1X in rational decision makers. It is an intuitive and widely held view that this computation or extraction of an abstract prospective value signal can motivate goal-directed behavior by acting as a representation of the future value of some outcome to be obtained (Glimcher and Rustichini, 2004; Louie and Glimcher, 2012). The catch lies in the interpretation of ‘abstract’. Do these signals indeed represent abstracted, model-free representations of value in a common currency, or is some aspect of the stimulus configuration predicting the outcome retained in a model-based outcome representation³ (Levy and Glimcher, 2011; Padoa-Schioppa, 2011; Schoenbaum et al., 2011; McDannald et al., 2012)?

Electrophysiological recordings of OFC neurons
This debate on the nature of OFC neural representations stems from the observation that single neurons recorded from the OFC show spiking activity changes that are time-locked to stimulus and reward presentations. Thorpe et al. (1983), recording from macaques, already noted that some of these neurons’ responses to an invariant stimulus are in themselves plastic and can change according to (the value of) the outcome linked to the stimulus in the face of the invariant stimulus being presented. Adding to the evidence in

³McDannald et al. (2012) provide a compelling analogy: assuming that a doughnut has a certain equivalent value in dollars, an expected monthly payout of salary based on a model-free representation of said salary does not differentiate between a paycheck and a cart full of doughnuts, whereas a model-based representation allows differentiation on the basis of the actual properties of the outcome besides its equivalent value.
favor of ‘abstract value representations’, Schoenbaum and colleagues, using a 4-odor discrimination task, found that of the population of OFC neurons that showed firing patterns during cue sampling that discriminated between the odors predicting positive versus the odors predicting negative outcome, some did not discriminate between the actual odor *exemplars* indicating the same outcome, while others responded only to one specific odor exemplar (Schoenbaum et al., 1999). However, responses of rat OFC neurons did not necessarily signal value in an absolute, transitive sense, because separate subpopulations of OFC neurons showed elevated firing rates in relation to positive or negative outcome (sign differences) in 2 outcome tasks (Schoenbaum et al., 1999; Roesch et al., 2006) and non-monotonic, sometimes intransitive response profiles in a 5-outcome odor discrimination task (van Duuren et al., 2007a, 2008). Subsequent recording studies from rat orbitofrontal studies, including those from our lab, have reliably reported subpopulations of neurons (generally about 20% by statistical criteria) sensitive to cue-outcome configurations during stimulus sampling. Moreover, these studies indicated that rat OFC neuronal responses were sensitive to manipulations of reward delay, magnitude, probability and other parameters that could affect the subjective value attached to the cues (Schoenbaum et al., 1998; Roesch et al., 2006; van Duuren et al., 2007a, 2009; Kepecs et al., 2008).

These findings contrast with a line of electrophysiological studies in primate OFC where subpopulations of multi-unit activity (MUA, spikes recorded from more than one neuron) have been found to encode decision variables such as offer value, chosen value and outcome in an abstract “goods space” in a parametric, transitive and range-adapting fashion. This means that differences in the encoding of one prospective value associated with a stimulus versus another were correlated with actual choice behavior and revealed preferences in a neureconomic framework that resembles findings in humans (Padoa-Schioppa and Assad, 2006, 2008; Kable and Glimcher, 2009; Padoa-Schioppa, 2009, 2011; Levy and Glimcher, 2011; Louie and Glimcher, 2012). Other groups have confirmed that primate OFC (mostly central OFC, areas 11 and 13, see Fig.1.1b) responses follow the domain generality (i.e. code outcomes in a common currency), sign-specificity and modulation by behavioral context as predicted from this model (Roesch and Olson, 2005; Kennerley et al., 2009; Morrison and Salzman, 2009), though
the regression slopes capturing the variation along the value axis could be consistently positive or negative for different neurons. However, it seems that the proportion of neurons that integrates multiple decision variables in its response profile, as if coding value in a common currency, is relatively small: the coding of reward magnitude and reward variance (risk of obtaining either a low or high reward with the same probability) was found in largely separate pools of neurons, though these parameters interact in choice behavior (Kennerley et al., 2009; O’Neill and Schultz, 2010; Schultz et al., 2011).

In humans, activity of orbitofrontal cortex in relation to economic value signals is recorded using fMRI. A large body of research indicates that these hemodynamic activity signals vary parametrically with subjective value in the ventromedial prefrontal cortex (vmPFC or mOFC, see Gottfried et al., 2003; Kable and Glimcher, 2007; Hare et al., 2008; Rangel and Hare, 2010; Noonan et al., 2011; Rushworth et al., 2011 and many others). We have to be careful in drawing parallels between primate electrophysiological recordings and human neuroimaging results. For one, the blood oxygenation level-dependent (BOLD) signal is thought to reflect mainly synaptic activity, while single unit recordings report action potentials whose probability of occurrence is modulated by, but does not strictly follow, those synaptic inputs (Logothetis et al., 2001; Logothetis, 2003). The main locus of value-based BOLD signals (vmPFC) is considered to be a granular area analogous to the macaque area 14 (mOFC), and therefore distinct from the usually reported central OFC subregions 11/13 (cOFC, Mackey and Petrides, 2010; Wallis, 2012). vmPFC BOLD signals reflect domain generality (coding different outcomes in a common currency), scaling in activation along the negative-to-positive subjective value axis. Furthermore, delay, risk, effort (or opportunity costs) and even exercised willpower can modify value-related signals in vmPFC (Kable and Glimcher, 2007; Christopoulos et al., 2009; Hare et al., 2011; Schultz et al., 2011).

One view, emerging from the combination of comparative lesion studies in macaques and regional fMRI analyses, is that the more lateral aspects of OFC are involved in keeping track of and updating stimulus-outcome associations, while more medial aspects are involved in making fine-grained comparisons between the value of response options, presumably to inform the decision-making process (Rushworth et al., 2011; Schoenbaum et al., 2011; Wallis and Kennerley, 2011). Supporting this notion, lesions of IOFC affect
value based stimulus discrimination and responding when reward variance is high (i.e. outcomes differ greatly between cues, and credit assignment failures lead to suboptimal performance), whereas mOFC lesions affect decision making between more closely matched outcomes (Noonan et al., 2010; Walton et al., 2010; Mar et al., 2011).

**OFC reward-related signals: value or prediction errors?**

OFC value-related signals are not only present when outcomes are delivered (tracking the relative pleasantness derived from the outcome (Kringelbach et al., 2003), but also in anticipation of these outcomes as ‘predicted outcome’ signals. Such outcome related firing patterns are also found in many other areas of the frontal cortex and in subcortical structures, such as the amygdala (Schoenbaum et al., 1998; Roesch and Olson, 2004; Roesch et al., 2007b). However, in contrast to most other structures, the representations in the OFC are already present in the anticipatory period, after cue sampling but before outcome delivery and in the absence of outcome-predicting cues - earlier than in other structures, and are therefore thought to represent the current expectation of outcome (Wallis and Miller, 2003). This feature of OFC coding fits nicely with theoretical models of reinforcement learning, such as Temporal Difference Reinforcement Learning (TDRL) models (Schultz et al., 1997; Sutton and Barto, 1998; Pennartz et al., 2011b). In such models, learning takes places maintaining a value representation of expected outcome V(t) over time until the actual outcome is delivered and by subsequent updating of synaptic weights based on the discrepancy between predicted and actual outcome (Reward Prediction Error (RPE), Rescorla and Wagner, 1972). There is still debate whether (bi-directional) RPE signals are present in OFC or not (Schoenbaum et al., 2009; Takahashi et al., 2009; Sul et al., 2010); even if they are, recent research has made the case that the role of the OFC lies primarily in helping to update the associative value of cues in other regions, such as the basolateral amygdala (BLA) or ventral striatum (VS), with which it is densely interconnected, by providing expected outcome information that can be entered in RPE calculations implemented in other areas (Carmichael and Price, 1995a; Öngür and Price, 2000; Stalnaker et al., 2007; Schilman et al., 2008). Following the argument by Schoenbaum (2009), the outcome expectancy signals broadcasted by OFC are required for efficient RPE calculations in downstream areas such as ventral striatum and/
Chapter 1. GENERAL INTRODUCTION

or VTA (Hare et al., 2008; Rolls et al., 2008; Takahashi et al., 2009). Indeed, DA-releasing neurons recorded in the VTA encode bi-directional RPEs with their firing rate, and the generation of these putative neuronal correlates of RPEs depends on functional connectivity with ipsilateral OFC (Schultz et al., 1997; Roesch et al., 2007a; Takahashi et al., 2011). Presumably, these RPE signals could then be used as teaching signals to alter synaptic weights in stimulus-outcome associations in more primary valuation areas such as BLA or areas implementing the role of critic (including Ventral and Dorsal Striatum [VS/DS]) in TDRL models (Sutton and Barto, 1998; McDannald et al., 2011, 2012; Pennartz et al., 2011b). In reversal learning tasks, maintenance of OFC pre-reversal neural cue-outcome association representations, rather than rapidly updated associations, was found to be predictive of better performance in the reversal stage, presumably because the old expected outcome signals generate large RPEs that drive efficient stimulus-outcome remapping in other areas (Stalnaker et al., 2006; Schoenbaum et al., 2007). In support of this presumed cross-structural role of the OFC in reversal learning, OFC lesion-induced impairments of reversal learning can be lifted by lesioning or inactivating the ipsilateral BLA (Stalnaker et al., 2006; Schoenbaum et al., 2007). These observations are in line with a concept of strong RPE signals being required, after reversal, to quickly alter now maladaptive representations in areas implementing the roles of actor and critic (Hare et al., 2008; Schoenbaum et al., 2009, 2011). OFC could provide the model-based expected outcome signal that is an essential input to RPE calculations.

This argument makes predictions for the role of inter-structural communication in calculating RPEs. Factors that increase the precision, strength and/or impact of the expected outcome output signal from the OFC to areas implementing RPE calculations should improve RPE calculation (e.g. Takahashi et al., 2011) and thereby performance in reversal-learning situations. Rhythmic synchronization of neuronal activity within and between areas is a proposed key mechanism for efficient information transfer across different parts of the brain, and one of the main topics of investigation in this thesis. The next paragraph examines the research underlying the hypothesis that rhythmic synchronization of OFC units could be instrumental in the efficient broadcasting of expected outcome information.
Rhythmic synchronization

Rhythmic activity is ubiquitous in the mammalian central nervous system: whether we examine EEG or MEG measurements of human volunteers or single-electrode recordings made in rodents or primates, virtually everywhere scientists record neural activity, oscillatory patterns appear. Perhaps the most well known rhythmic patterns of the brain are the EEG rhythms, recorded from the human scalp, classified into certain frequency bands: the alpha rhythm with a periodicity of about 10 cycles per second (10 Hz), apparent over the visual cortex when participants close their eyes; the slower delta rhythm (1-4 Hz) that is present during deep sleep (also called ‘slow wave sleep’) and the gamma rhythm (generally defined by frequency bounds of 30-100 Hz, though subdivisions are now recognized) that appears to scale in amplitude with cognitive effort (e.g. Fitzgibbon et al., 2004; Buzsáki, 2006). Invasive electrophysiological recordings in such diverse species as rodents, cats and primates have confirmed the existence of these rhythms in many cortical and subcortical areas, in hippocampus, thalamic and brainstem nuclei (Wang, 2010). In humans undergoing neurosurgery, invasive electrophysiological recordings show similar oscillatory patterns, though the exact frequency band can differ between species (e.g. Canolty et al., 2006). The temporal dynamics of synaptic currents, recurrent inhibition and the resulting membrane potential fluctuations of single neurons also show resonating properties, which means that most neurons are maximally sensitive to rhythmic, patterned input with preferred frequencies (Llinas, 1988; Hunter et al., 1998; Pike et al., 2000; Deans et al., 2007; Klausberger and Somogyi, 2008; Cardin et al., 2009; Wang, 2010). Lower-frequency rhythmic activity entrains larger populations of neurons (also across brain regions), and, as a consequence, amplitudes of those low-frequency oscillations are also larger (Varela et al., 2001; Buzsáki and Draguhn, 2004). An interesting feature of this organization or scale of frequency bands is that the possibility exists for frequencies to interact with each other, in a way that the phase of lower frequencies modulates the amplitude of the higher frequency band. This “nesting” of frequencies or phase-amplitude coupling is introduced separately below. In rodents, two of the most frequently studied rhythms are the theta (6-12 Hz) and gamma (30-100 Hz) rhythms. As both rhythms were

This and the following sections were modified from parts of a recent review by Pennartz, van Wingerden & Vinck (2011)
Chapter 1. GENERAL INTRODUCTION

also studied as part of this thesis, a slightly more extensive introduction on their physiology in the next paragraphs is warranted.

**Theta-band synchronization**

One of the earliest descriptions of the theta rhythm dates back to Vanderwolf in the sixties. The theta rhythm is the most prominent rhythm found in the rodent hippocampus, and is readily visible during explorative behavior (Vanderwolf, 1969; Buzsáki, 2002). It is thought to play a role in the encoding and retrieval of spatial and episodic memory in humans and rodents (Kahana et al., 1999; Buzsáki, 2005; Hasselmo, 2005; Canolty et al., 2006; Addante et al., 2011; Burgess and O’Keefe, 2011). Furthermore, LFP oscillatory phase synchronization of slow (~1-12 Hz) rhythms, such as the theta rhythm is hypothesized to implement functional interactions between areas over large anatomical distances (Siapas et al., 2005; Buzsáki, 2006; DeCoteau et al., 2007; Paz et al., 2008; Pesaran et al., 2008; Schroeder and Lakatos, 2009; Benchenane et al., 2010; Wang, 2010; Womelsdorf et al., 2010). Strong coherence, a consistency in phase relationships between sites, in combination with a ‘good’ phase relationship, may allow distant neuronal ensembles to interact, while taking conduction delays into account, promoting cross-structural information transfer (Fries, 2005, 2009; Womelsdorf et al., 2007). In this context the “goodness” of the phase is defined by the efficacy of communication. LFP slow rhythm ‘hypersynchronization’ between large parts of the brain is a hallmark of epilepsy – a reminder that more synchrony is not always better (Perez Velazquez and Carlen, 2000). Womelsdorf et al. (2010) argued that the key cognitive function supported by selective theta synchronization is the “structured retrieval of choice-relevant information around decision points”, and suggested that distributed theta oscillatory states across brain areas are involved in successful retrieval of these task-relevant representations of stimulus-outcome relationships and contextual rules. In addition, theta-band synchrony has been proposed to subserve the read-in and initial storage of information in higher sensory and associational areas, including the hippocampus (Buzsáki, 2005; Battaglia et al., 2011; Benchenane et al., 2011). In the context of the proposed network function of the OFC, it stands to reason that slow rhythmic activity could be involved in coupling the areas involved in stimulus evaluation (cf. Fujisawa and Buzsáki, 2011; Lesting et al., 2011; van der Meer and Redish, 2011). We
have investigated OFC rhythmic synchronization in the theta band during an olfactory decision-making task, the results of which are reported in Chapter 2.

**Gamma-band synchronization**
The high-frequency, low-amplitude gamma-band rhythm (30-100 Hz) can readily be found throughout the mammalian nervous system (Gray et al., 1989; Eeckman and Freeman, 1990; Bragin et al., 1995; Wehr and Laurent, 1996; Fries et al., 2001; Brosch et al., 2002; Pesaran et al., 2002; Schoffelen et al., 2005; Bauer et al., 2006; van der Meer and Redish, 2009; Cardin et al., 2009; Kalenscher et al., 2010). Accumulating evidence suggests that gamma-band synchronization plays an important role in selective attention (Fries, 2009; Gregoriou et al., 2009), can increase the speed and efficiency of information transmission (Taylor et al., 2005; Womelsdorf et al., 2006; Hoogenboom et al., 2010) and sub serves sensory processing and assembly formation (Singer, 1999; Fries et al., 2007; Rotermund et al., 2009; Siegel et al., 2009; de Almeida et al., 2009; Vinck et al., 2010a; Wang, 2010; Buzsáki and Wang, 2012). There is increasing consensus that gamma-band synchronization in cortical structures emerges from a recurrent interplay between pyramidal cells and specific subtypes of interneurons, among which the fast spiking basket cell that delivers perisomatic inhibition to pyramidal cells via the release of the neurotransmitter GABA (Gamma-aminobutyric acid; Bartos et al., 2007; Cardin et al., 2009; Sohal et al., 2009; Tiesinga and Sejnowski, 2009; Wang, 2010; Buzsáki and Wang, 2012; Whittington et al., 2012). In models of this interaction, gamma oscillations originate from the activity of pyramidal cells that drives the activation of local interneurons through axon collaterals with a short delay. In turn, the basket cells inhibit the activity of pyramidal cells and by corollary also their own excitatory input. Consequently, the pyramidal cells are released from inhibition and spiking activity can increase, shortly followed by a next cycle of inhibition. This type of network structure is dubbed a ‘PING’ network and seems to be most in agreement with experimental data (reviewed in Bartos et al., 2007; Tiesinga and Sejnowski, 2009) though the alternative, a self-organizing interneuron driven synchronization or ING network cannot be ruled out, especially for neural regions that lack strong excitatory connections such as the cerebellum (Wang, 2010; Buzsáki and Wang, 2012; Whittington et al., 2012) and in
Chapter 1. GENERAL INTRODUCTION

fact both mechanisms might interact to generate gamma rhythms over the wide frequency range included in this class of rhythms. In many sensory cortical areas, gamma-band synchronization is induced by the activation of pyramidal cells by sensory stimuli (Gray and Singer, 1989; Fries et al., 2001; Brosch et al., 2002; Kay, 2003; Bauer et al., 2006; Beshel et al., 2007). The role of gamma-band synchronization in higher cognitive function has been less well documented, though a clear relationship with working-memory processes has been established (Tallon-Baudry et al., 1998; Raghavachari et al., 2001). It has been hypothesized that gamma synchronization is a fundamental property of cortical computations, reflecting possibly local network computations such as input normalization or gain control (Fries, 2009; Ray and Maunsell, 2010); it seems therefore prudent to investigate the role of gamma band synchronization in OFC-dependent computational processes, such as the stimulus-based expected outcome value retrieval step discussed above. Our studies of OFC gamma band synchronization are presented in Chapter 3.

Cross-frequency interactions

The ratio of theta and gamma frequency oscillations (amongst a range of possible pairs) allows for phase-amplitude interactions, where the phase of the slower oscillation determines the probability of a bout of the faster oscillation. This phenomenon of cross-frequency coherence has been observed within and between brain regions, and could serve several computational goals that involve assembly formation (entraining activity from neurons in different brain areas in an ensemble so they tend to fire ‘as one’) such as working memory and pattern separation (Varela et al., 2001; Buzsáki and Draguhn, 2004; Fries, 2005; Jensen and Lisman, 2005; Canolty et al., 2006, 2010; Cohen et al., 2009a; Schroeder and Lakatos, 2009; Canolty and Knight, 2010). In the OFC, one could speculate that cross-frequency phase-amplitude coupling may occur when input from afferent regions is read in and feeds into the proposed local stimulus valuation computation. We investigated the interactions between OFC theta and gamma band rhythmic processes during stimulus sampling and the results are described in Chapter 5.

Neurotransmission in orbitofrontal networks

As in most parts of the cortex, the main excitatory neurotransmitter in OFC
Box 2 A material memory trace: the NMDA-receptor and synaptic plasticity

Adopting the materialist view that the mind is made up of brain processes, we can view the idea of memory as a lasting change in the structure of the mind as necessarily being instantiated by concomitant changes in the brain. The synaptic theory of memory does just that: building on the work by anatomists such as Ramon y Cajal and Golgi, Donald Hebb postulated an influential theory (Hebb, 1949) that allowed for the selective strengthening of neuron-to-neuron connections if both cells are synaptically connected and active simultaneously. A large body of work confirmed this principle of association in vivo (e.g. Bliss and Lomo, 1973; Morris et al., 1986; Davis et al., 1992; Bailey et al., 2000; Johansen et al., 2011; see Caporale and Dan, 2008 for a review). The molecular basis of this theory was discovered next: simultaneous activity of pre- and postsynaptic cells in many structures of the mammalian CNS activates a certain type of voltage-gated sodium channel called the \textit{N-methyl-D-aspartate or NMDA-receptor}, named after its selective chemical agonist, though in vivo, the activating compound is the excitatory neurotransmitter glutamate, that also acts as agonist on the non-voltage gated AMPA and metabotropic glutamate receptors. Strong depolarization of the postsynaptic membrane in tandem with chemical activation of the NMDA-R enables the influx of calcium (and sodium) ions into the postsynaptic neuron: this signal starts a molecular signaling cascade that ultimately results in the recruitment of more AMPA-receptors into the postsynaptic density. The higher number of AMPA-Rs enhances the responsiveness of this particular synapse to presynaptic activity by allowing a larger postsynaptic influx of sodium ions through AMPA-receptors binding glutamate that is released into the synapse (Kandel et al., 2000). This persistent enhancement of responsiveness is called long-term potentiation or LTP (though other means to elicit LTP, not requiring NMDA-Rs, do exist (Derrick and Martinez, 1996; Galván et al., 2008). Its counterpart, long-term depression or LTD, also seems to require NMDA-Rs. Here, the precise timing of pre- and postsynaptic activity appears to play a role in setting the directionality of synaptic plasticity in a process called \textit{Spike-Timing Dependent Plasticity or STDP} (see main text).
networks is glutamate (released from afferent synapses and OFC pyramidal cell local recurrent synapses), while GABA, released preferentially from interneurons, provides inhibition to the network. Indeed, local perfusion of GABA-receptor agonists was found to inhibit OFC spiking (van Duuren et al., 2007b). Effects of intra-OFC modulation of neuromodulators (such as dopamine and serotonin [DA/5-HT]) on OFC-dependent tasks have also been described. For example, in a delay-discounting task where rats choose between a sooner, smaller reward and a larger, later reward, task performance selectively increases OFC dopamine turnover, as measured by microdialysis (Winstanley et al., 2006). Blocking D1 receptors in OFC decreases impulsive responding on the 5-choice serial reaction time test (Winstanley et al., 2010), though OFC probably is not directly involved in action inhibition (Chudasama et al., 2007; Eagle and Baunez, 2010). 5-HT innervation of the OFC comes mainly from the dorsal raphe nucleus, which in turn also receives backprojections from OFC that are thought to mediate feedback control over the release of 5-HT (Gonçalves et al., 2009). Depleting 5-HT or blocking its postsynaptic receptors in rodent and marmoset OFC induces deficits in performance on tasks involving a reversal, particularly in inhibiting a response to previously rewarded, but now unrewarded stimuli (reviewed in Roberts, 2011). Roberts (2011) suggested that forebrain 5-HT levels could reflect expected outcomes, following inputs from OFC. Reduced 5-HT levels would then lead to reduced outcome expectations and thus to reduced RPEs following non-reward after reversal, making animals less likely to abandon habitual responding to previously rewarded cues.

**NMDA-receptor mediated plasticity of OFC network activity**

The N-methyl-D-aspartate or NMDA-receptor (NMDA-R) is required for bi-directional long-term changes in synaptic plasticity (LTP/LTD, see Box 2; Lisman, 1994; Selig et al., 1995; Lee et al., 1998; Malenka and Nicoll, 1999).

The precise timing of pre- and postsynaptic action potentials can lead to selective strengthening or weakening of synapses allowing a synapse-specific, Hebbian-compliant way of synaptic modification called Spike-Timing Dependent Plasticity or STDP (Bi and Poo, 1998; Abbott and Nelson, 2000; Cassenaer and Laurent, 2007; Caporale and Dan, 2008; Markram et al., 2011), and in this context, precise timing of spiking activity of pre- and
postsynaptic neurons between structures via phase-locking mechanisms for long-range synchronization are particularly interesting (see General Discussion). The involvement of the NMDA-R in cognitive function is well established, especially in the areas of spatial and emotional memory (Morris et al., 1986; Li et al., 1995; Kentros et al., 1998; Ekstrom et al., 2001; Goosens and Maren, 2004; McHugh et al., 2007) and working-memory operations (Lisman et al., 1998; Wang, 1999; Durstewitz et al., 2000; Seamans et al., 2003; McHugh et al., 2008). As the putative computational roles of the OFC in stimulus-outcome learning involve associative learning, pattern separation (e.g. eliciting separable neural ensemble activity patterns by stimuli that are to be discriminated for subsequent go/nogo action patterns) and working memory components (in maintaining a value signal online), it can be conjectured that blocking NMDA-R activity will interfere with one or more hallmarks of OFC neural coding. The data speaking to this hypothesis are further explored in Chapter 4.

**Aim and Outline of the thesis**

In this thesis, I will describe the role of rhythmic synchronization and NMDA-R mediated plasticity in value-related neural signals recorded from rat orbitofrontal cortex during a two-odor discrimination task. These experiments and analyses have been performed with the valuable help of a number of colleagues. Therefore, I will refer to “we” when describing these experiments. Though the initial observation of this rhythmic activity in our recordings was serendipitous, we quickly engaged in a number of hypotheses and analyses that are presented in this thesis. In Chapter 2, the role of theta-band synchronization in orchestrating expected outcome information in OFC will be discussed. We present evidence for a locally generated theta rhythm that, during an anticipatory period before outcome delivery, correlates with current outcome expectancies as apparent from the behavior of the rat. In Chapter 3, the role of theta and gamma-band synchronization during stimulus evaluation and decision-making is discussed. In the behavioral task that we used, rats are required to make a go/nogo decision based on the odor available on a given trial. In this task, gamma-band activity during odor sampling appears to reflect a more general computational process that correlates with parameters of learning extracted from behavior and involves primarily cells that do code expected outcome at a later locomotor task stage, when the rats traveled
Chapter 1. GENERAL INTRODUCTION

from odor port to fluid well where outcomes were delivered. In Chapter 4, our data on NMDA-R mediated effects on shaping the characteristic neural activity patterns of OFC described in the previous chapters is presented. In essence, blocking NMDA-Rs distorts rhythmic synchronization and prevents plasticity in OFC single neuron outcome-selective activity from building up. The interaction between theta and gamma rhythmicity is investigated in Chapter 5. Phase-amplitude coupling of theta and gamma rhythms was shown to be specific for the stimulus evaluation phase, and correlated with correct decisions (Hits and Correct Rejections). The strength of phase-amplitude coupling on these trials increased with learning. Decision periods on trials with bad outcomes showed reduced phase-amplitude coupling. 

Chapter 6 provides a general discussion of these exciting results in the light of previously published data and some suggestions for further steps.