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Reviews and perspectives

Neuropsychological assessment of the orbital and ventromedial prefrontal cortex

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ABSTRACT

Assessment of the functions of the orbitofrontal cortex and ventromedial prefrontal cortex has proven to be a unique challenge for neuropsychologists. Orbitomedial damage occurs in a range of disorders including traumatic brain injury, ruptured aneurysms, surgical resection, and frontotemporal dementia. We review the effects of orbitomedial damage on a range of neuropsychological tasks, including tasks measuring object alternation and reversal learning, decision-making (gambling), facial emotion recognition, theory of mind, olfactory recognition, autobiographical memory and behavioral rating measures. At present, there is no singular gold standard measure of orbitomedial dysfunction, and assessment requires an integrative approach that reflects the heterogeneity of the region. The heterogeneous neuropsychological deficits arising from orbitomedial damage are difficult to ascribe to a unitary function or process, but appear to reflect a set of processes necessary for monitoring and adapting to changing reinforcement contingencies.

Contents

1. Introduction

Identifying and assessing the functions of the orbitofrontal cortex (OFC) and ventromedial prefrontal cortex (VMPFC) has proven to be a unique challenge for neuropsychologists. At a superficial

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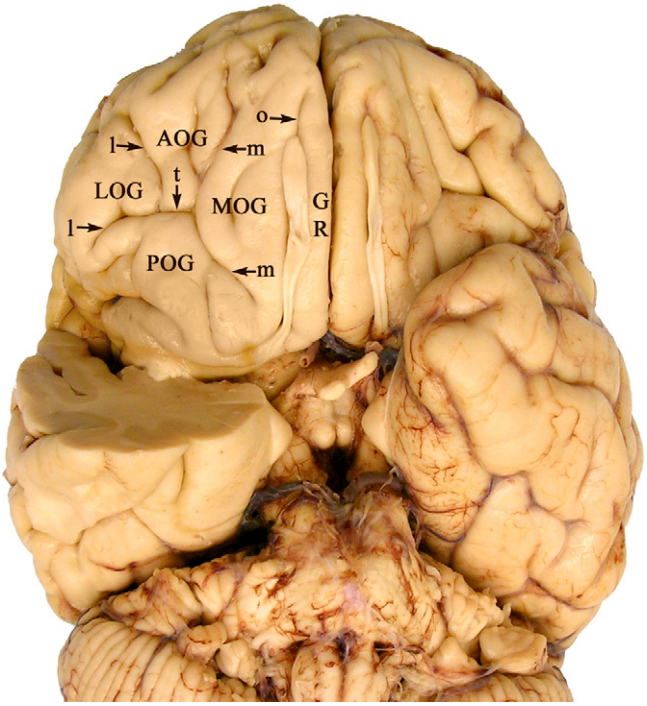

Fig. 1. Macroscopic view of the ventral surface of the human brain, with the temporal lobe resected in one hemisphere to reveal the entire orbitofrontal surface. The figure is adapted with permission from Gottfried and Zald (2005), and is based on a specimen prepared by Dr. Eileen H. Bigio, Dept. of Pathology, Northwestern University Feinberg School of Medicine, Chicago, IL at the request of Dr. Jay Gottfried. The capitalized labels denote orbital gyri: LOG = lateral orbital gyrus; POG = posterior orbital gyrus; AOG = anterior orbital gyrus; MOG = medial orbital gyrus; GR = gyrus rectus. The lower case labels with arrows denote sulci: l = lateral orbital sulcus; t = transverse orbital suclus; m = medial orbital sulcus; o = olfactory sulcus. Note there are two arrows to denote lateral and medial orbital sulci reflecting the rostral and caudal branches of these sulci, which are divided based on their position relative to the transverse orbital suclus. Most of the olfactory sulcus is hidden by the olfactory bulb. Additional fragmentary and intermediary sucli can be seen in this sample, but are not labeled because they are inconsistently expressed across individuals.

level, individuals with dysfunction in these regions often appear cognitively intact, even demonstrating normal performance on standard neuropsychological batteries. Yet, the deficits associated with ventral frontal damage can cause disastrous consequences, not infrequently leading to major interpersonal, occupational and legal problems. In the present paper we review the neuropsychological literature on the effects of ventral frontal damage in humans. In doing so, we aim to both evaluate the diagnostic utility of existing measures purported to tap the functions of the OFC and VMPFC, and to highlight the implications of these findings for further elucidating the specific functions of the region.

2. Anatomy of the OFC and VMPFC

The OFC comprises the ventral surface of the prefrontal cortex (PFC). Although several specific gyri and sulci are identifiable in the OFC (see Fig. 1), most of the neuropsychological literature in humans, generically labels damage to any of these gyri as OFC damage, or makes use of broad labels such as poster, anterior, medial or lateral OFC.

The VMPFC is centered along the inferior portion of the medial wall of the frontal lobe. The exact boundaries of this region are not always defined, but the superior boundary can be roughly defined as a line running from the genu of the corpus callosum. The area below this line includes the subgenual cingulate (subcallosal area), the ventral part of the pregenual cingulate, and the ventromedial part of the frontal pole (see Fig. 2). As typically applied in the clinical literature, the VMPFC region partially overlaps with the medial parts of the OFC, either including the gyrus rectus, or both the gyrus rectus and the medial orbital gyrus as part of the VMPFC. Because this regional designation overlaps with the medial OFC, and pathologies affecting the region often affect both the OFC and overlying aspects of the ventromedial wall simultaneously, it is difficult to segregate these areas in the clinical literature. Indeed, papers reporting VMPFC damage almost always include patients with damage to the medial aspects of the OFC, and studies reporting on medial OFC lesions often include patients with damage to the overlying cortex along the medial wall. Although there are clearly cytoarchictural and connectional differences between medial wall and OFC regions (Price, 2006), there is also a fair degree of overlap near the intersection of these regions. For instance, the posterior gyrus rectus has significant connections with neighboring medial orbital areas as well as extensive connections to the overlying subgenual cingulate (Carmichael & Price, 1996). While the central focus of a lesion (medial wall vs. orbital surface) almost certainly has an impact on the functions disrupted by the lesion, it remains difficult in group studies to fully disentangle the relative contributions of the OFC and ventral medial wall based on the clinical literature in isolation. Throughout the remainder of the review, we use the term orbitomedial (OMPFC) to refer to the combination of the OFC and VMPFC territories. In places we retain use of the terms OFC and VMPFC to provide greater topographical precision, although the reader may nevertheless wish to treat the VMPFC/OFC distinction with some caution, as this often reflects a predominant location of damage rather than an isolated or dissociable focus of damage.

3. Sources of OMPFC damage

Several types of neuropathology produce damage to the OMPFC in humans. These range from closed head injuries and penetrating head wounds, to cerebrovascular accidents, tumors, neurosurgical excisions, and neurodegenerative disorders. Because such conditions vary widely in terms of their pattern of impact within the OMPFC and the degree to which they impact neighboring brain regions, it is useful to briefly consider the general features of damage caused by these conditions.

Patients with OMPFC damage as a consequence of closed head injury are relatively common in typical neuropsychology clinics. However, such patients are often not the most informative from a research standpoint, because the damage is rarely specific to the OMPFC and frequently involves substantial damage to the frontal and temporal poles (Courville, 1937), as well as more widespread axonal shearing (Pang, 1989). Nevertheless, advances in MRI techniques allow increasing quantification of the relative degree of focal and diffuse injury (Parizel et al., 1998; Levine et al., 2008).

Patients with surgical excisions in the OMPFC (e.g., for removal of tumors or epileptogenic tissue) often have quite restricted lesions, although the size of the excisions and the degree of specificity to the OMPFC varies in such cases. In some patients there may be continued disturbance in functioning of the remnant tissue surrounding the excised tissue or tumor. To the extent that the lesions impinge upon white matter, they may also disrupt fibers of passage. Yet, when the extent of the lesion is well characterized, and no additional pathology is present, patients with surgical excisions provide some of the best opportunities to examine the effects of OMPFC lesions in isolation.

A variety of different types of tumors can infiltrate the OMPFC. Olfactory groove meningiomas arising from the dura around the cribiform plate and frontal sphenoidal suture are among the most notable, due to their frequency. At first, these tumors may be relatively "silent" in their effects, with noticeable symptoms only arising after the meningioma has grown to occupy a large intracranial volume (Gazzeri, Galarza, & Gazzeri, 2008).

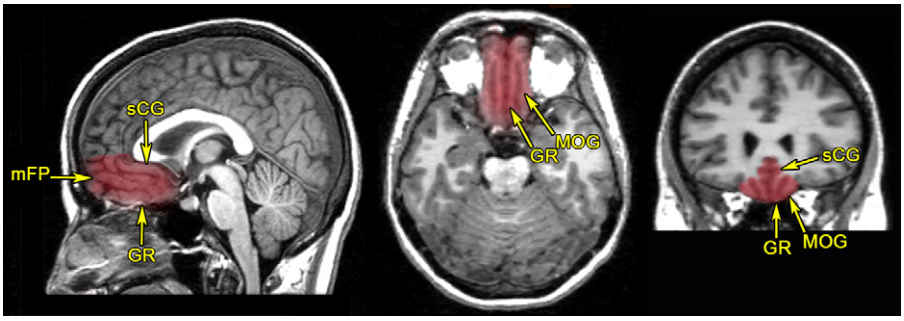

Fig. 2. T1 weighted MRI showing a sagittal and axial view of the VMPFC (designated in red). Although the exact boundaries of the VMPFC are variably applied in the literature, it can include the entire medial wall ventral to the genu of the corpus callosum, and may extend laterally into the medial orbital gyrus.

Cerebrovascular accidents are also a common source of injury to the OMPFC. The vascular supply of VMPFC derives from the leptomeningeal portion of the anterior cerebral artery, including the orbital branch (or branches), which serves the gyrus rectus and medial orbital gyrus, and the frontopolar branch, which serves the anterior OFC and medial frontal pole (Tatu, Moulin, Bogousslavsky, & Duvernoy, 1998). In contrast, the lateral aspects of the OFC are served by the orbital branch of the middle cerebral artery. Critically, the anterior communicating artery (ACom) traverses the posterior-medial OFC, and is a frequent location of ruptured aneurisms. Indeed this is among the more common sources of damage to the posterior OMPFC. ACom aneurism can lead to three types of damage: (1) the hemorrhage itself will cause damage, (2) in many cases endovascular surgeons will resect a portion of the gyrus rectus in order to gain access to the aneurysm, and (3) in the process of clipping the aneurysm, vessels coming off the ACom may also be cut (DeLuca & Diamond, 1995).

Among neurodegenerative disorders, the frontal variant of frontotemporal dementia (fvFTD: also known as dementia of the frontal lobe type or the behavioral variant of frontotemporal dementia) is unique in the prominence of the disruption of OMPFC processes (Lu & Cummings, 2006). However, the pathology of fvFTD is by no means limited to the OMPFC, and frequently involves other frontal regions, particularly more dorsomedial regions (Franceschi et al., 2005; Varrone et al., 2002; Williams, Nestor, & Hodges, 2005). Thus, while providing general support for OMPFC involvement in tasks, fvFTD cannot be considered to reflect a "pure" OMPFC pathology, and in some cases the deficits may very well reflect disruption of other frontal circuits.

4. Toward a neuropsychology of the OMPFC

The functions of the OMPFC have at times been described as enigmatic. While some of this enigma arose because of a lack of specific tasks tapping the region in the early development of neuropsychology, we suspect that the divergent nature of tasks that are sensitive to OMPFC damage has also contributed to the continued difficulty conceptualizing the functions of the region. At least five themes arise in the types of neuropsychological tasks that are sensitive to OMPFC damage: (1) an ability to utilize cues in the environment to predict future rewarding or aversive events; (2) an ability to regulate behavioral responses, particularly in the context of changing reinforcement contingencies; (3) specific aspects of social processing, (4) olfactory processing and (5) autobiographical memory. This characterization is by nature broad, and the specific tasks tapping such processes are quite varied. Indeed, as reviewed below, the details of the tasks appear critical in determining whether the OMPFC is actually essential to carry out a given process.

At present there is no "gold standard" measure of OFC or VMPFC function. Rather, there exist a number of measures that have demonstrated sensitivity (and in a few cases specificity) to the effects of lesions in the OMPFC. Most of these tasks derive from experimental literatures, because traditional neuropsychological assessment batteries are generally insensitive to OMPFC damage (Anderson, Damasio, Tranel, & Damasio, 1992; Angrilli, Palomba, Cantagallo, Maietti, & Stegagno, 1999; Eslinger & Damasio, 1985; Stuss et al., 1983). Indeed, part of the "enigma" of the OMPFC has been the field's difficulty explaining the real-life problems experienced by OMPFC lesion patients given their appearance of normality on most neuropsychological tests. In contrast, several experimental measures and nonstandard clinical measures have proven quite sensitive to OMPFC damage. We review these below. We particularly focus on tasks and functional domains in which there have been at least two papers on the same or related tasks in patients with OMPFC neuropathology. Where appropriate, we also comment on issues of specificity, which are critical in considering if the tasks are tapping a truly unique function of the OMPFC, and for determining the potential diagnostic utility of the measures.

5. Learning and adapting to changing reinforcement contingencies

The broadest group of cognitive tasks showing sensitivity to OFC lesions involve tasks in which the individual must learn a reward contingency that diverges from expectation or that is changing over time. In his seminal 1964 chapter on the OFC, Mishkin (1964) put forth the hypothesis that animals with OFC lesions have a "perseveration of central sets" in which they are unable to overcome or inhibit prepotent responses. Both object alternation (OA) and object reversal learning (ORL) tasks demonstrate this perseverative characteristic, and as such provide a critical starting point for understanding OMPFC lesion effects in both monkeys and humans.

5.1. Alternation tasks

In OA tasks, subjects view two objects, and on a trial-by-trial basis, must select whichever object they did not select on the previous trial. The relative position of the objects varies randomly, so that the subject must rely on object features in making their response selections. The task was originally developed as a complement to spatial alternation tasks in which the spatial location alternates from trial to trial (Pribram & Mishkin, 1956). Studies with monkeys demonstrated marked deficits in the reacquisition of OA following lesions to the lateral OFC or inferior convexity (Mishkin & Manning, 1978; Mishkin, Vest, Waxler, & Rosvold, 1969; Pribram & Mishkin, 1956). Strikingly, lesioned monkeys often showed no improvement in task performance even after thousands of trials. In essence, the monkeys appeared unable to relearn the task rule. The effect appeared specific to more ventral frontal lesions, as

animals with lesions centered above the inferior convexity were largely unimpaired on the task. Mishkin interpreted the deficit as reflecting a perseveration of central sets, because the monkeys appeared unable to overcome an apparent bias against adopting the necessary win-shift strategy and instead appeared to maintain an assumed preportent nonfunctional strategy.

Impairments in OA acquisition been demonstrated in humans with ventral frontal lesions. In a study by Freedman, Black, Ebert, and Binns (1998), six patients with bilateral frontal lesions performed an OA task in which they had to learn the task rule through trial and error learning. Consistent with the animal literature, the frontal lesion patients showed significantly more errors than the controls on OA acquisition. More recently, in a study of 58 patients with traumatic brain injury, OA task performance was sensitive to ventral frontal lobe damage. Although these studies converge with the animal literature, it must be noted that OA acquisition appears to lack specificity as a strict index of ventral frontal functioning (Fujiwara, Schwartz, Gao, Black, & Levine, 2008). In the Fujiwara study, volume loss in superior medial frontal regions was predictive of OA deficits, and in the Freedman study, patients had large lesions that extended into both the frontal pole, and more dorsomedial regions.

PET data also support the involvement of the OFC in OA. Ventral frontal activations have been observed during both the acquisition and the practiced performance of OA tasks (Curtis, Zald, Lee, & Pardo, 2000; Zald, Curtis, Folley, & Pardo, 2002; Zald, Curtis, Chernitsky, & Pardo, 2005). However, the neuroimaging data also raises questions regarding the specificity of OA tasks to the OFC. As with many "frontal lobe" tasks, the neuroimaging data indicate that multiple areas become active during both the acquisition and practiced performance of OA (Curtis et al., 2000; Zald et al., 2002, 2005; Turner & Levine, 2006) including more robust and large activationa of the pre-supplementary motor area (pre-SMA), dorsal anterior cingulate and dorsolateral PFC regions.

Lesions to the lateral OFC/inferior convexity region in monkeys have also been reported to impair *spatial* alternation (Mishkin et al., 1969), and existing evidence suggests a similar involvement in humans (Freedman & Oscar-Berman, 1986; Turner & Levine, 2006). However, at least in monkeys, the spatial alternation deficits appear more variable than the impairments in OA (Passingham, 1975). Furthermore, spatial alternation is robustly impaired following more dorsally placed lesions (especially in the principal sulcus region) due to the spatial working memory demands of the task (Butters & Pandya, 1969; Goldman, Rosvold, Vest, & Galkin, 1971; Mishkin, 1957; Mishkin et al., 1969; Passingham, 1975). Because of the involvement of DLPFC regions, spatial alternation is not believed to have the same localizing specificity as OA.

5.2. Reversal learning

A number of monkey lesion studies have demonstrated impairments in ORL following OFC lesions (Butter, 1969; Butters, Butter, Rosen, & Stein, 1973; Dias, Robbins, & Roberts, 1996; Iversen & Mishkin, 1970; Meunier, Bachevalier, & Mishkin, 1997; Mishkin & Manning, 1978; Passingham, 1975; Rudebeck & Murray, 2008; Voytko, 1985). In ORL tasks, an animal is rewarded with food for selecting an object until reaching a certain criterion level performance after which the reward contingency reverses so that the previously rewarded object is no longer rewarded, and the previously nonrewarded stimulus becomes the rewarded stimulus. Depending upon the specific paradigm, the reward contingency may undergo a single reversal, or may undergo multiple reversals, with the reversals occurring every time the subject has reached a certain criterion performance level. The most prominent reversal deficits arise as a sequela of inferior convexity lesions, and appear to be part of a general problem with perseveration (Iversen & Mishkin, 1970). More centrally located lesions (areas 11 and 13) do not produce as consistent effects (Butter, 1969; Kazama & Bachevalier, 2009), although some data suggest that they can when the lesions extend into or are focused on the gyrus rectus (Izquierdo, Suda, & Murray, 2004; Meunier et al., 1997; Kazama & Bachevalier, 2009). In some cases, particularly when the lesions include more medial OFC lesions, the deficit appears more related to an inability to update which item was rewarded on a trial-by-trial basis. In these cases, the deficit only arises after both stimuli have been associated with reward and nonreward (Butter, 1969; Voytko, 1985). A simple associative process alone cannot be used for determining which stimulus is the correct one to respond to in this situation because both stimuli have been associated with reward and nonreward. Rather, similar to the OA task, the animal must be able to hold on line in working memory information about which object is currently rewarded, and which object is not rewarded. However, in reversal tasks, knowledge of when to switch objects can only be determined based on the receipt of error feedback. While deficits in spatial reversals have also been noted in monkeys with OFC lesions, they are significantly more inconsistent, and thus used less frequently in human populations (Butter, 1969; Butters et al., 1973; Passingham, 1975; Goldman et al., 1971).

Human subjects with OMPFC damage have been repeatedly found to exhibit deficient performance on reversal tasks (Berlin, Rolls, & Kischka, 2004; Fellows & Farah, 2003; Hornak et al., 2004; Rolls, Hornak, Wade, & McGrath, 1994). It should be noted that the specific tasks have varied substantially from study to study (e.g. Fellows & Farah, 2003; Rolls et al., 1994). Patients with VMPFC lesions performed significantly worse than both healthy control participants and patients with DLPFC lesions, whereas patients with DLPFC performed no worse than healthy controls, providing evidence for the specificity of the lesion. This task may be useful in distinguishing between dorsolateral and VMPFC patients, and is consistent with data from monkeys in this regard (Dias et al., 1996).

In studies using a more complex "probabilistic reversal task" (e.g. Berlin et al., 2004; Hornak et al., 2004) in which object probability and reward value slowly reversed over the course of the task, deficits only occurred in patients with bilateral OMPFC lesions, as patients with unilateral lesions performed normally. In terms of specificity, patients with medial prefrontal lesions (Brodmann areas 8 and 9) performed normally. The performance of patients with DLPFC lesions was highly variable, with some showing normal performance and others showing performance as bad as the OMPFC patients. However, post-test screening revealed that the DLPFC patients who performed poorly had all failed to attend to the feedback information, making it virtually impossible for them to perform the task properly. In contrast, the patients with bilateral OMPFC damage reported that they understood the need to pay attention to the feedback screen, but nevertheless were unable to perform the task properly. In a second paper (Berlin et al., 2004), the authors found that a combined group of patients with both unilateral and bilateral OMPFC lesions were significantly impaired on the task relative to both healthy controls and to patients with frontal lesions that did not encroach upon the OMPFC. In both studies, the OMPFC patients who were impaired on the task appeared relatively insensitive to the outcome of trials,

The Cambridge Neuropsychological Test Automated Battery (CANTAB: Cambridge Cognition, Cambridge, UK) contains a well-normed and standardized measure of reversals as part of the ID/ED (intradimensional/extradimensional shift) task. This task attempts to capture the dissociation observed in studies of marmosets in which more ventral frontal lesions lead to impaired affective (reward–nonreward) reversals within a dimension, whereas more dorsolateral lesions lead to problems with extradimensional shifting (changes in the type of stimulus features that need to be responded to) (Dias et al., 1996). Unfortunately, data specifi-

cally testing this dissociation in humans with well-defined frontal lesions remains limited. The strongest support at present comes from a study of fvFTD. Rahman, Robbins, and Sahakian (1999) reported that these patients show a specific deficit in the reversal phase of the ID/ED task, while demonstrating intact performance on nonreversal components on the task. The patients further performed normally on tasks that are sensitive to DLPFC lesions, consistent with the idea of a relatively selective ventral frontal involvement in these fvFTD patients.

Neuroimaging data on ORL supports the involvement of the lateral OFC/ventrolateral prefrontal region during reversal learning (Cools, Clark, Owen, & Robbins, 2002; Kringelbach & Rolls, 2003; O'Doherty, Critchley, Deichmann, & Dolan, 2003; Remijnse, Nielen, Uylings, & Veltman, 2005). These studies frequently utilize probabilistic ORL tasks in order to make the tasks sufficiently challenging for healthy controls, and so most parallel the work of Hornak and colleagues described above. In addition to the VLPFC, the studies also frequently demonstrate involvement of the anterior cingulate region. While specific data addressing the effects of cingulate lesions on ORL in humans remains lacking, data from a primate lesion study suggests a greater importance of the OFC than the cingulate for ORL but not spatial reversal learning. Animals with lesions to OFC or cingulate show differential performance over the course of the task, with OFC lesioned animals exhibiting increased errors compared to animals with cingulate lesions, especially on later reversals. These differences disappeared when a spatial discrimination task was used (Meunier et al., 1997). These findings appear consistent with the alternation literature in indicating a greater ability to discriminatively detect OFC dysfunction in tasks requiring attention to object rather than spatial features of the stimuli.

Failure of ORL appears related to a number of other deficits in patients with ventral frontal lobe lesions. For instance, Rolls et al. (1994) indicate a relationship between errors on their probabilistic ORL task and behavioral ratings by staff members regarding the degree to which subjects were socially inappropriate and disinhibited. Similarly, Fellows and Farah (2003) observed an inverse association between simple ORL performance and ratings of independent activities of daily living.

5.3. Wisconsin card sort

From a theoretical perspective, if participants with OMPFC lesions have problems acquiring task rules, or adapting to changing reinforcement contingencies, one might expect them to also perform poorly on the Wisconsin Card Sort Task (WCST), which involves trial and error learning and rule changes. However, patients with OMPFC lesions show no increases in perseverative errors relative to controls on the WCST (Stuss et al., 2000). They do, however, tend to complete fewer sorting categories, primarily due to a failure to maintain set (i.e., they fail to stick with a sorting rule that is working) (Stuss et al., 2000, 1983). The lack of perseverative errors on the WCST (and analogous tests in animals) indicates that the OFC is not broadly necessary to suppress all classes of perseverative responses. Given the work of Diaz and colleagues (Dias et al., 1996), it appears that the OFC is particularly important when acquiring simple ORL, but not the more abstract rules changes that are assessed by the WCST, which appear more dependent on more dorsal PFC regions.

5.4. Response inhibition

Models of frontal lobe functions have often emphasized the importance of behavioral inhibition, and indeed an early literature developed suggesting a contribution of the OFC to response inhibition. Go/NoGo tasks provide a classic measure of response inhibition, which requires the subjects to suppress a response on nogo trials, despite a prepotent go response that is established through a far greater frequency of go than nogo trials. Brutkowski and Davrowska (1963) demonstrated that lesions of the OFC in monkeys produced impaired inhibition responses on nogo trials. Subsequent studies in monkeys with more focal lesions demonstrated that the deficit arose following lesions of the inferior convexity (lateral OFC and ventral principal sulcus region) (Butters et al., 1973; Iversen & Mishkin, 1970) but not following lesions to more medial orbital areas (Butter, 1969; Iversen & Mishkin, 1970). Based on these animal data, some investigators have argued for the use of the Go/NoGo task as a measure of OFC functioning in humans. Potential support for the use of Go/NoGo tasks in the assessment of ventral frontal function comes from a study of healthy controls by Spinella (2002), who reported correlations between Go/NoGo performance and measures of delayed alternation and olfactory performance (see discussion below on olfactory functions). The human lesion literature provides clear evidence that prefrontal lesions cause problems inhibiting responses on nogo trials (Black et al., 2000; Drewe, 1975; Godefroy & Rousseaux, 1996; Leimkuhler & Mesulam, 1985; Salmaso & Denes, 1982). Deficits have also been observed in patients with fvFTD (Slachevsky et al., 2004). Support for inferior frontal involvement in Go/NoGo impairments comes from a study of schizophrenic patients who had undergone prefrontal leukotomies, which cause particularly strong damage to the afferents and efferents of ventral frontal regions (Black et al., 2000). However, the remainder of the human lesion literature provides little evidence for a specific OFC source of the deficit and focus on the effects of other PFC regions on commission errors (Drewe, 1975; Godefroy & Rousseaux, 1996; Leimkuhler & Mesulam, 1985; Picton et al., 2007; Swick, Ashley, & Turken, 2008).

A relatively large neuroimaging literature has emerged in recent years on response inhibition tasks including Go/NoGo tasks, suggesting that to the extent Go/NoGo deficits reflect frontal damage, they may be a better measure of ventrolateral functioning than that of the OFC proper or VMPFC (Aron & Poldrack, 2005; Hooker & Knight, 2006; Swick et al., 2008). Neuroimaging data also indicate some variability in the extent to which Go/NoGo tasks engage the inferior frontal gyrus. Simmonds, Pekar, and Mostofsky (2008) recently reported the results of a meta-analysis of neuroimaging studies using Go/NoGo tasks. The analysis confirmed involvement of the inferior frontal gyrus, but suggested that inferior frontal gyrus activations mainly arises in complex rather than simple Go/NoGo paradigms, and that the activation is more consistent in a more dorsal sector of the inferior frontal gyrus than suggested by Aron and colleagues. Moreover, the meta-analysis found that the most common activation in Go/NoGo studies arises in the pre-SMA region. Taken together, the neuroimaging literature indicates the importance of dorsomedial and ventrolateral regions as opposed to the OMPFC in Go/NoGo performance.

6. Decision-making (gambling) tasks

In recent years, intense interest has developed on the potential use of gambling tasks as probes for VMPFC dysfunction. This line of inquiry stems from the repeated anecdotal observation of poor, and often risky, decision-making in patients with OMPFC lesions (Eslinger & Damasio, 1985; Harlow, 1868). Unlike the experimental tasks described already, gambling tasks have emerged strictly within the context of studies of human patients. The Iowa Gambling Task (IGT) is the most widely used of these tasks. Developed by Bechara, Damasio, Damasio, and Anderson (1994), the task requires subjects to choose between four decks of cards: A, B, C and D. On each trial, patients choose a card resulting in a monetary reward or loss. Decks A and B provide a large payout on each choice but also

an occasional large loss. Decks C and D provide a small payout on each choice, but rarer small losses. Across a block of trials, selecting from decks C and D is advantageous in that they result in a net win. In contrast, decks A and B are disadvantageous in that they result in a net loss. Subjects are not instructed about the reward and punishment contingencies of each deck, but are instructed that some of the decks are "better" than others. Thus subjects have to implicitly or explicitly acquire information about the reward contingencies through trial and error learning. The primary measure of interest from the IGT is the extent to which subjects select from disadvantageous card decks.

Evidence supports the sensitivity of the IGT to VMPFC lesions, at least when the lesions include the right VMPFC (Bechara et al., 1994; Bechara, Damasio, Tranel, & Anderson, 1998; Tranel, Bechara, & Denburg, 2002). The effects of left OMPFC lesions have been less clear. Floden, Alexander, Kubu, Katz, and Stuss (2008) found that riskier, less advantageous strategies were related to left ventrolateral and orbital damage. In contrast, other studies have found that lesions restricted to the left VMPFC region (or left OFC more generally) do not lead to riskier deck selections on the IGT (Manes et al., 2002; Tranel et al., 2002). Performance has also been demonstrated to be impaired in fvFTD (Torralva et al., 2007; Torralva, Roca, Gleichgerrcht, Bekinschtein, & Manes, 2009).

Serious questions remain regarding the specificity of the IGT. Whereas early data from Bechara et al. (1998) suggested normal performance of patients with DLPFC lesions, data from studies by Manes et al. (2002) and Clark, Manes, Nagui, Sahakian, and Robbins (2003) indicate significant effects of lesions that include either dorsolateral or dorsomedial PFC regions. The variability of DLPFC effects may relate to the laterality of the lesions, with a greater right than left hemisphere involvement in the task (e.g. Clark et al., 2003; Levine et al., 2005).

Neuroimaging data supports the engagement of the VMPFC in healthy normals performing the IGT relative to control conditions but also suggests that other PFC areas including frontopolar, dorsolateral and dorsomedial regions play a role in the task (Ernst et al., 2003). Event related fMRI allows examination of activity in relation to specific aspects of the task. Importantly, prefrontal activity emerges when healthy participants select cards from riskier decks (Fukui, Murai, Fukuyama, Hayashi, & Hanakawa, 2005). However, this activation localizes to a relatively dorsal area along the anterior medial wall (roughly 2 cm above the intercommissural plane) rather than a ventromedial region. Fellows and Farah (2005) have suggested that the disadvantageously risky card selections on the IGT shown by VMPFC lesion patients may relate not to a specific deficit in decision-making but from a more elemental deficit in reversal learning, as indicated by improved performance when the initial bias favoring the disadvantageous decks is removed by reordering the cards. Poor performance on the IGT is often characterized as reflecting an insensitivity to risk. However, the learning and explicit reversal components of this task leave unclear whether it is actually tapping risk processing per se. The most widely used alternative to the IGT is the Cambridge Gambling Test (Rogers et al., 1999), which explicitly provides probabilities on each trial, thus avoiding any requirement for learning from previous trials. On each trial the subject views a number of colored squares and determines whether a token is under a blue square or a red square. The probability is reflected in the number of blue or red squares appearing for the given trial. After seeing the number of red and blue squares, the subject is first asked to make a probabilistic judgment of whether the token is under one of the blue or red squares, and then is asked to determine how much they want to bet that they are correct. In an initial study, Rogers et al. (1999) reported that patients with OMPFC lesions were impaired in their probabilistic judgments and made suboptimal bets compared to healthy controls. In contrast, subjects with dorsomedial frontal lesions appeared normal. The most convincing data on the effects of VMPFC lesions on the CGT comes from a study by Clark et al. (2008) who observed a bias towards risky betting in 20 patients with VMPFC damage (50% bilateral), without a deficit in probability judgments. Other studies of lesion patients and patients with fvFTD have not provided as consistent support for either the sensitivity or the specificity of the CGT, or have suggested subtle deficits in probabilistic reasoning rather than a generalized insensitivity to risk (Clark et al., 2003; Mavaddat, Kirkpatrick, Rogers, & Sahakian, 2000; Rahman et al., 1999). In terms of specificity, it is also notable that Clark et al. (2008) describe an insensitivity to risk in patients with insular damage, consistent with fMRI data implicating the insula in risk-averse decision-making (Kuhnen & Knutson, 2005; Paulus, Rogalsky, Simmons, Feinstein, & Stein, 2003; Venkatraman, Payne, Bettman, Luce, & Huettel, 2009).

Outside of specific tasks like the CGT and IGT, a rich literature on the neural substrates of risk has developed over the last decade. These data support the importance of VMPFC regions in aspects of decision-making related to risk, but also raise some interpretational questions. For instance, supporting a role of the VMPFC in anticipation of adverse events, the VMPFC appears engaged when individuals anticipate the presence of a predator in a video game (Mobbs et al., 2007). However, the engagement of the VMPFC does not in itself predict more risk-averse decision-making, as might be predicted from the neuropsychological patient data. To the contrary, several studies indicate that increased risk seeking or reward maximization follows from increased activation of VMPFC regions (Kuhnen & Knutson, 2005; Tobler, O'Doherty, Dolan, & Schultz, 2007; Venkatraman et al., 2009). These neuroimaging findings support the involvement of the VMPFC in decision-making, but are difficult to reconcile with a view that the VMPFC is central to inhibiting risky decisions. Interestingly, an fMRI study by Tobler et al. (2007) suggests that it is actually more lateral OFC areas that are predictive of more risk-averse decision-making. This raises the question of whether some of the effects reported for VMPFC patients might be due to the inclusion of patients whose lesions extend into more lateral OFC areas.

Techniques such as transcranial magnetic stimulation (to suppress activity) and transcranial direct current stimulations (to enhance activity) have also been used to study risk taking. These techniques cannot be directly applied to the OMPFC, but can be used to modulate DLPFC functioning. Both transcranial magnetic stimulation and transcranial direct current stimulation over the DLPFC (particularly in the right hemisphere) have been found to modulate risk-taking behavior on tasks in which subjects can win or lose money (Fecteau, Knoch, et al., 2007; Fecteau, Pascual-Leone, et al., 2007; Knoch et al., 2006). These data provide further support that areas of the PFC beyond the VMPFC contribute to decision-making related to risk.

In summary, a growing literature supports the importance of the VMPFC in decision-making, and several tasks appear sensitive to VMPFC lesions. However, a number of complexities must be considered in using these tasks, including confounds related to reversal learning, and issues related to regional specificity.

7. Social processing and theory of mind

Facial expressions are a critical aspect of human nonverbal communication of emotion. A number of neuroimaging studies involving explicit judgments about faces implicate the OFC in aspects of facial judgments (Dougherty, Shin, & Rauch, 2006). However, the importance of the OFC to emotional recognition of facial expressions is unresolved. Large lesions that include the OFC have been observed to cause deficits in facial emotion recognition (Blair & Cipolotti, 2000; Heberlein, Padon, Gillihan, Farah, & Fellows,

2008; Hornak, Rolls, & Wade, 1996; Hornak et al., 2003; Marinkovic, Trebon, Chauvel, & Halgren, 2000; Shamay-Tsoory, Tomer, Berger, & Aharon-Peretz, 2003). A sizable literature also indicates problems with emotional recognition in patients with fvFTD (Fernandez-Duque & Black, 2005; Keane, Calder, Hodges, & Young, 2002; Lavenu & Pasquier, 2005; Lavenu, Pasquier, Lebert, Petit, & Van der, 1999; Lough et al., 2006; Rosen et al., 2004), although the effect does not appear to consistently differentiate between fvFTD and other dementias. In the lesion studies, deficits have been observed both with prototypical faces and faces morphed to show varying degrees of emotion, and with both forced-choice and rating tasks. However, not all studies have observed deficits (or deficits relative to other patient groups). In some cases, this may relate to stimulus characteristics, as some studies have suggested that recognition of particular sets of emotions may be more sensitive to OMPFC damage than others (i.e., Beer, John, Scabini, & Knight, 2006; Blair & Cipolotti, 2000; Marinkovic et al., 2000). Across studies, deficits in recognizing negative emotions arise more often than problems with positive emotions. However, the precise emotions showing sensitivity is not completely consistent across studies, and may reflect methodological issues related to specific task demands (see Heberlein et al., 2008 for discussion). The location of lesions may also be important. For instance, Hornak et al. (2003) observed normal performance in a forced-choice study of 6 patients (5 right hemisphere) with circumscribed unilateral OFC excisions. However, the majority of the unilateral participants had damage that does not overlap with the most common foci of activation in the neuroimaging studies [which tend to localize to more lateral OFC and frontal opercular areas (Dougherty et al., 2006), rather than the extreme posterior-medial and anterior regions that characterize many of Hornak's unilateral patients]. Such data raise the possibility that emotional recognition tasks could be differentially sensitive to the location of OMPFC lesions, although the methodological differences across existing studies precludes drawing firm conclusions about subregional localization of emotional recognition.

Theory of mind (ToM) refers to the ability to make inferences regarding the mental state (knowledge, intentions, and beliefs) of others. Multiple neuroimaging and electrophysiological studies (see Gallagher & Frith, 2003; Sabbagh, Moulson, & Harkness, 2004 for reviews) and studies of patients with frontal lobe dysfunction (Gregory et al., 2002; Lough et al., 2006; Rowe, Bullock, Polkey, & Morris, 2001; Shamay-Tsoory & Aharon-Peretz, 2007; Shamay-Tsoory, Tomer, & Aharon-Peretz, 2005; Shamay-Tsoory, Tomer, Berger, Goldsher, & Aharon-Peretz, 2005; Stone, Baron-Cohen, & Knight, 1998; Stuss, Gallup, & Alexander, 2001) indicate a general association between ToM deficits and the frontal lobes. Of particular interest in the present context is the ability to detect *faux pas* types of social blunders. Recognition of faux pas involves an element of ToM in that it requires the subject to infer what the persons involved in a scenario did or did not know at the time of incident, as well as emotional mentalizing of how the people in the scenario feel. Individuals with damage to OMPFC exhibit deficits in faux pas detection relative to healthy controls and individuals with more posterior cortical lesions (Shamay-Tsoory, Tomer, Berger, et al., 2005; Stone et al., 1998). Gregory et al. (2002) and Torralva et al. (2007, 2009) similarly observe deficits in faux pas detection in subjects with fvFTD. In the Gregory study, the number of ToM tasks that were compromised (including the faux pas task + other ToM tasks, such as false belief tasks) was associated with a rating of the amount of VMPFC atrophy observable on MRI. Torralva et al. (2007, 2009) similarly observe additional ToM deficits [(the Reading in the Minds Eye Test (Baron-Cohen, Jolliffe, Mortimore, & Robertson, 1997)] and note the sensitivity of ToM measures to deficits in early stages of the disorder when other executive function tasks still appear normal. Lough et al. (2006) also report diminished performance on ToM tasks in patients with fvFTD (in this case tasks related to cartoon jokes requiring mentalizing, and moral judgments). While general cognitive abilities were diminished in this sample, ToM performance remained independent of these changes. It is notable that, at least to date, the ToM deficits in fvFTD appear more widespread than those seen in lesion patients. For instance, Shamay-Tsoory, Tomer, Berger, et al. (2005) indicate that their patients can perform false belief tasks, and suggest that the observed ToM deficits are primarily related to affective (as opposed to cognitive) mentalizing, the fvFTD patients appear deficient on false belief tasks that are not strictly affective in nature.

To date, the only other lesion site that has been associated with deficits on the Faux Pas Recognition Task is the amygdala (Stone, Baron-Cohen, Calder, Keane, & Young, 2003). The similarity of this effect to the deficit arising from ventral frontal damage is consistent with the tight anatomical and functional connections between the amygdala and OMPFC (Zald & Kim, 2001).

In considering the faux pas recognition deficit arising from ventral frontal lesions, it is useful to note that these deficits generally do not occur in isolation, and may be accompanied by deficits in detecting irony, sarcasm, and deception (Shamay-Tsoory & Aharon-Peretz, 2007; Shamay-Tsoory, Tomer, Aharon-Peretz, 2005; Shamay-Tsoory, Tomer, Berger, et al., 2005; Stuss et al., 2001). In each case these deficits appear worse following VMPFC (particularly right VMPFC) lesions relative to more dorsal (particularly DLPFC regions). These deficits are also likely accompanied by measurable deficits in scales tapping empathy (Lough et al., 2006; Rankin, Kramer, & Miller, 2005; Shamay, Tomer, & Aharon-Peretz, 2002; Shamay-Tsoory, Tomer, Goldsher, Berger, & Aharon-Peretz, 2004; Shamay-Tsoory, Aharon-Peretz, & Perry, 2009), a finding which converges with the frequent emergence of OMPFC activations during empathic and emotional perspective taking responses (Farrow et al., 2001; Hynes, Baird, & Grafton, 2006; Lamm, Nusbaum, Meltzoff, & Decety, 2007), Such findings are consistent with fMRI studies that implicate the OMPFC, present data indicate that empathy deficits in isolation are probably not particularly specific to the OMPFC as these deficits occur with reasonable frequency both in patients with right parietal lesions and patients with semantic dementias (Rankin et al., 2005; Shamay-Tsoory et al., 2004).

In summary, although the literature on faux pas recognition and the recognition of irony, sarcasm, and deception remains limited, the data so far are encouraging, and suggest a critical social processing component of OMPFC functions. Inclusion of such measures may prove useful when augmenting a neuropsychological test battery to focus on ventral frontal functions, and may be relevant for understanding the real-life social problems exhibited by patients with OMPFC lesions.

8. Olfactory testing

The OFC receives substantial input from the olfactory system, and is often described as secondary olfactory cortex (Carmichael, Clugnet, & Price, 1994). The strongest olfactory projections are located in the posterior OFC, but neuroimaging data demonstrates that multiple areas of the OFC are responsive to odorants (Gottfried & Zald, 2005). Although olfactory functioning has often been overlooked as a major focus of clinical neuropsychology, the existing data suggest that it is among the most sensitive and selective measures of OFC dysfunction.

Olfactory processing deficits frequently arise in cases of OMPFC damage, both due to simultaneous damage to the olfactory bulb or nerve (which are vulnerable to trauma), or due to damage directly to secondary olfactory cortex. In the first instance, a general anosmia demonstrated by deficient olfactory detection thresholds occurs (Varney, 1988), whereas damage to secondary olfactory cor-

tex impairs other types of olfactory judgments. The most widely used standardized measures of olfactory functioning is the University of Pennsylvania Smell Identification Test (Doty, Shaman, Kimmelman, & Dann, 1984). On each item of this test, participants scratch a microencapsulated odorant, and then indicate which of four choices the odor smells like. The strongest data supporting the UPSIT's sensitivity to OFC functions derives from a study by Jones-Gotman and Zatorre (1988), who examined 120 patients with focal surgical brain lesions. Among frontal lobe lesion patients, impairments only emerged in subjects whose lesions invaded the OFC, suggesting an ability to discriminate between ventral frontal vs. other frontal lesions. Patients with unilateral temporal lobectomies also demonstrated impairments, although these were significantly weaker than patients with OFC lesions. Thus, although not completely specific relative to anterior temporal lesions, the data suggest that particularly severe deficits are indicative of OFC damage. Similar deficits in smell identification have been observed in studies of patients with ruptured ACoM aneurysms (Martin et al., 2009). Fujiwara et al. (2008) note that smell identification performance was more closely linked to grey matter changes in the ventral frontal cortex than either OA or IGT performance.

Patients with FvFTD also demonstrate impairments on the UPSIT, which are unlikely to be due to damage to the olfactory bulbs or nerves (Pardini, Huey, Cavanagh, & Grafman, 2009), although it may be noted participants with other types of dementia also show impairments on this measure possibly due to more temporal dysfunction (Luzzi et al., 2007; Pardini et al., 2009). Deficits in olfactory recognition performance also arise in multiple sclerosis, and appear related to measured levels of plaques in the ventral frontal and temporal olfactory regions (Doty, Li, Mannon, & Yousem, 1998; Doty, Li, Mannon, & Yousem, 1999; Zorzon et al., 2000).

Right OFC damage also results in deficits in olfactory discrimination (Hulshoff Pol et al., 2002; Potter & Butters, 1980; Zatorre & Jones-Gotman, 1991). Importantly, these studies indicate a critical difference between temporal lobe and frontal lesions on olfactory discrimination. Temporal lobectomies only impair discrimination on the nostril ipsilateral to the lesion site. In contrast, right OFC lesions cause a birhinal deficit in olfactory discrimination. This represents a clear-cut distinction between the effects of temporal lobe and OFC damage on olfactory functions, and may be useful when trying to discriminate between two potential sources of olfactory deficits.

8.1. Memory

The OMPFC has substantial connections with the medial temporal lobes. The subiculum provides a direct projection into multiple portions of the OMPFC (gyrus rectus, medial orbital gyrus, subgenual and posterior pregenual cingulate), while the entorhinal cortex is bidirectionally connected to both the VMPFC as well as the more laterally situated area 12o) (Price, 2006). In humans, neuroimaging studies have observed OFC activations in specific memory tasks (Brand & Markowitsch, 2006; Elliott & Dolan, 1999). Based on these connections and activations, it might be predicted that lesions of the OMPFC would impact performance on memory tasks. However, most traditional neuropsychological measures of memory (such as the various versions of the Wechsler Memory Scale) appear normal in patients with selective OMPFC lesions. When deficits in memory performance do arise in such cases they often appear in a manner that suggest a failure to properly learn and utilize tasks rules or overcome interference (Chase et al., 2008) rather than a pure deficit in memory encoding or retrieval.

Nevertheless, relatively severe memory problems do sometimes arise as part of the clinical picture in some patients with lesions encompassing the OMPFC (DeLuca, 1993; Stuss et al., 1982). The most dramatic of these involve patients with "Acom syndrome", which involves a combination of personality change and memory deficits with prominent confabulations arising as a consequence of an Acom aneurysm (Alexander & Freedman, 1984). However, the amnestic symptoms do not appear to reflect damage to the OMPFC, but rather arise as a consequence of damage to proximal structures in the basal forebrain, particularly the cholinergic neurons of the basal nucleus of Meynert (Bottger, Prosiegel, Steiger, & Yassouridis, 1998; DeLuca, 1993). Nevertheless, the emergence of confabulation may direct attention to the OMPFC, as confabulation appears substantially more common after OFC lesions than lesions of other frontal areas, with lesions involving inferior sections of the cingulate providing the second most frequent source of confabulations (Turner, Cipolotti, Yousry, & Shallice, 2008). Such confabulations in OFC patients appear particular prominent in response to questions that probe personal episodic material (Turner et al., 2008).

Consistent with the literature on confabulation, Brand and Markowitsch (2006) suggest that the OMPFC is particularly involved in retrieving autobiographical episodic memories, with an emphasis on emotional episodes and memory for context. The most developed attempt to assess this domain in the neuropsychological literature comes from work by Levine and colleagues who developed the Autobiographical Interview (Levine, Svoboda, Hay, Winocur, & Moscovitch, 2002) in order to operationalize and quantify problems in retrieving autobiographical information. Patients with fvFTD dementia showed deficits on the measure, which stands in contrast to patients with dorsolateral prefrontal (DLPFC) lesions (Levine, 2004; McKinnon et al., 2008). A role for the OMPFC in retrieving autobiographical information is additionally supported by neuroimaging studies (Fujii et al., 2004; Svoboda, McKinnon, & Levine, 2006).

9. Interview and questionnaire data

Although cognitive and olfactory measures are sensitive to OMPFC dysfunction, they do not capture the range of real world abnormalities exhibited by patients with ventral frontal lesions. Because symptoms can occur in the absence of gross deficits on traditional neuropsychological measures, interview and questionnaire data provide essential information in assessing behavior that is not captured in the lab environment. Indeed, interview data characterizing changes in personality, disinhibition, and poor decision-making often provide the first hints of OMPFC dysfunction.

Several questionnaires and interview schedules are now available that capture some of the symptoms that have been anecdotally described in the clinical literature on OMPFC damage. Such measures are designed for administration to care givers or family members who rate the patient on a number of characteristics. A full characterization of these scales is beyond the scope of this review, but several warrant comment given the sorts of dysfunction that they tap. The Frontal Systems Behavioral Scale [FrSBe: originally titled the Frontal Lobe Personality Scale (Grace & Malloy, 2001; Grace, Stout, & Malloy, 1999)], is sensitive to frontal vs. nonfrontal damage and includes a Disinhibition scale that was specifically designed to capture purported symptoms of ventral frontal dysfunction Scores on the Disinhibition scale have been found to discriminate between FvFTD and Alzheimer's disease (Malloy, Tremont, Grace, & Frakey, 2007).

The Iowa Rating Scales for Personality Change, developed by Barrash and Anderson (1993) aims to capture aspects of personality change following frontal injury, and emphasizes a number of personality features specifically related to ventral frontal lesions. The scale includes items related to both changes in emotional functioning and real world competencies. Although normative data remains lacking for this scale, the authors have demonstrated that it has util-

ity in discriminating VMPFC patients from patients with nonfrontal lesions or more dorsal frontal lesions (Anderson, Barrash, Bechara, & Tranel, 2006; Barrash, Tranel, & Anderson, 2000). Anderson et al. observed significantly higher reports of emotional changes in the VMPFC group relative to patients with other frontal lesions, and patients with nonfrontal lesions. The VMPFC patients were rated both as having increased emotional reactivity (poor frustration tolerance, lability, irritability) and hypo-emotionality (impoverished emotions, apathy, blunted affect). Of note, although neither emotional reactivity nor hypo-emotionality is entirely specific to VMPFC lesions taken in isolation, the combination appears relatively unique to patients with VMPFC damage, suggesting a broad emotional dysregulation that includes both disinhition of some aspects of emotion, while having other domains in which the person seems to lack a typical emotional response.

Other interview measures in current use do not attempt to specifically identify a ventral frontal syndrome, but include items or subscales that assess specific behaviors associated with ventral lesions as part of a broader measurement of frontal pathology. For instance, the Frontal Behavior Inventory (Kertesz, Davidson, & Fox, 1997), which was developed to assess aspects of fvFTD, contains a number of questions specifically related to OMPFC pathology, including for instance inappropriateness, jocularity, impulsivity, aggression, and hypersexuality. The Neuropsychiatric Inventory (Cummings et al., 1994), which is one of the most widely used measures in the field, includes a number of items related to frontal pathology as part of a broader assessment of psychiatric symptoms arising in neurological conditions. For instance, items covering agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, appetite and eating abnormalities may all be of relevance for OMPFC patients. Other existing scales such as the Dysexecutive Questionnaire, which was developed in connection to the Behavioral Assessment of the Dysexecutive Syndrome test battery (Wilson, Alderman, Burgess, Emsley, & Evans, 1996) and the self-report Frontal Behaviour Questionnaire (Berlin et al., 2004), additionally capture problems related to impulse control, psychophysical and mental excitability, adherence to social conventions and the ability to incorporate social interaction in one's own behavior, that may be relevant to patients with ventral frontal damage.

10. Discussion

10.1. Functional implications

The above review of lesion effects on neuropsychological measures and behavioral rating scales indicates that a heterogeneous group of behaviors are affected by OMPFC lesions. This poses a significant challenge to attempts to define the OMPFC in terms of a singular theoretical or conceptual framework. Based on the different phylogenetic trends involving the OFC and medial frontal wall (Barbas, 1988), and the different connectional patterns of the ventral medial wall and OFC (Barbas & Pandya, 1989; Price, 2006), it should come as little surprise that there is functional heterogeneity within this region. Indeed, based on other techniques, such as single cell recordings and functional neuroimaging, there is evidence for functional dissociations between the OFC and the ventral medial wall. For instance, there is significantly greater evidence for chemosensory processing within the OFC than in the ventral medial wall (Gottfried, Small, & Zald, 2006), and more evidence for autonomic functions in the ventral medial wall than the OFC (Verberne & Owens, 1998). Nevertheless, it remains difficult to isolate a singular process within either of these trends that fully explains the range of deficits that arise from damage and theories of the OMPFC often focus on explaining only part of the clinical or experimental picture.

Theories that derive primarily from the human clinical literature often focus on attempting to explain the abnormal social behavior and behavioral disinhibition that characterize patients ventral frontal lobe lesions or FTDfv. For instance, a self-monitoring model has been posited to explain some of the behavioral abnormalities of OMPFC patients (Beer et al., 2006; Prigatano, 1991; Stuss and Benson, 1984; Stuss, 1991). This hypothesis is based on the idea that the OMPFC provides a constant on-line assessment of one's own behavior in order to align behavior with broad social goals and reactions. Within this framework, a lack of insight into the appropriateness of their own behavior leads to social blunders and poor behavioral control. In this context, the emotion recognition, faux pas and empathy deficits observed in OMPFC patients can be viewed as critical components necessary for self-monitoring of behavior in social interactions. Beer et al. (2006) provides some of the strongest evidence to date for this type of self-monitoring deficit, demonstrating that OMPFC patients have knowledge of social norms, but fail to monitor their behavior in relation to these norms. However, no attempt is made to explain the other deficits associated with OMPFC lesions, such as ORL, OA learning or olfactory deficits.

An alternative, although not mutually exclusive, model of OMPFC function focuses on the role of the OMPFC in inhibition. While OMPFC lesions do not cause a deficit in all forms of inhibition (as revealed by intact Go–NoGo performance), a failure to inhibit prepotent or motivated behavior is a recurrent theme in the animal and clinical literature (Mishkin, 1964). For instance, Plaisted and Sahakian (1997) posit an "inhibition hypothesis" to explain the deficits in social behavior that arise in patients with FTDfv and other patients with ventral frontal damage. They argue that these patients choose and initiate inefficient behavioral action plans due to an inability to inhibit their reaction to current environmental stimuli. When applied to the social and affective inputs to the OFC, this lack of inhibition causes the emotional quality of the current stimuli to unduly influence the behavioral response that is produced. Socially and behaviorally, this deficit prevents the selection of alternative and more appropriate action plans dictated by long-term goals. Hence behavior is dominated by the immediate emotional evaluation of the stimuli, regardless of any available emotional or somatic information about the consequences of more distal action plans.

Inhibition has also been posited to play an important role in certain cognitive tasks. For example, Dias, Robbins, and Roberts (1997) argue that ORL is impaired following OFC lesions due to a loss of inhibitory control in affective processing. In essence, the OFC is posited to be necessary to inhibit the affective value of the previously rewarded stimulus/reward pairing, thus maintaining the response to that no longer accurately valued stimulus. An inhibition hypothesis thus has the elegance of being able to explain both clinical behavioral abnormalities and some of the performance deficits on experimental behavioral tasks. A couple of caveats are warranted. First, for inhibition hypotheses to be useful it is critical to specify what is being inhibited. Dias et al. focus not on the response, but rather on the stimulus-reward association as the focus of the inhibition. Whether, it is the stimulus-reward association, or an emotional reaction, or a response itself that is inhibited has obvious implications for determining which types of tasks should be impaired by OMPFC damage, but this is not always clearly specified in the literature leaving unclear precisely which types of functions or tasks would be predicted to be vulnerable to OMPFC lesions. Other tasks that are sensitive to OMPFC lesions are also more difficult to ascribe to faulty inhibition. For instance, it is not clear why olfactory deficits or emotion recognition would be impaired by a failure of inhibition.

In order to more specifically explain which types of learning tasks are impacted by OFC lesions, other researchers have focused on the growing body of single cell (Peters & Buchel, 2010; Rolls,

2006; Roesch & Schoenbaum, 2006; Schultz & Tremblay, 2006; Wallis & Kennerley, 2010) and neuroimaging studies (O'Doherty & Dolan, 2006) of the OFC. For example, Rolls and Grabenhorst (2008: see also Rolls, 2004) theorize that the OFC's primary functional role lies in its ability to produce representations of expected reward values based on stimulus-reinforcer associative learning and the coding of prediction errors in which outcomes deviate from expectancy. Based on single cell data demonstrating the OFC cells are responsive to stimulus-reward learning processes, show responses consistent with knowledge of expected outcomes (expectancies), and respond when those outcomes do not arise (error coding), the OFC is argued to critically code changes in reinforcement contingencies in order to generate appropriate goals for actions. The ability to code such changes is essential for accurate performance during ORL tasks and the IGT in which initial contingencies change. Similarly, when contingencies do not conform to initial expectations, such as during OA learning, it is necessary to register deviations from expectation, and alter actions accordingly.

Within this stimulus-reinforcer associative learning framework, olfactory processing may be argued to be co-localized with other OFC processes because of the inherent importance of olfaction for signaling potential rewards or aversive experiences (such as good or rotten foods and prey or predators). Indeed, it may be argued that olfactory processing provided an important phylogenetic base from which broader stimulus-reinforcer processing developed. Importantly, a model that focuses on stimulus-reinforcer learning and valuation also provides a link to social processing in that social stimuli are a key class of reinforcers. Rolls and Grabenhorst do not explicitly attempt to explain behavioral disinhibition, but it may be presumed to arise within this model as part of a failure to integrate potential negative consequences in the valuation process.

Like Rolls and Grabenhorst (2008) and Schoenbaum and Esber (2010) provide a theoretical model of OFC functions that derives heavily from learning theory and animal single cell recordings. They argue that the OFC is part of a network of structures that signals information about expected outcomes, with the OFC providing the critical ability to integrate information in real-time to make actionable predictions or estimates about future outcomes. The OFC is proposed to be especially critical for signaling information about the precise outcomes that can be expected in a particular situation. In other words, the coding must be highly context and situation dependent, as simple associations between a single stimulus and a reward do not provide enough information for generating expectancies across different situations. This emphasis on context is consistent with the proposed involvement of the OMPFC in context memory and autobiographical episodic memory, which have not been typically incorporated to conceptual models of OMPFC functioning. In contrast, the social processing deficits observed in OFC patients have not been specifically treated within this framework, although as noted by Rolls and Grabenhorst, they may be relevant as social reinforcers.

Rushworth, Behrens, Rudebeck, and Walton (2007) provide a view of OFC functions that is largely compatible with the view of OFC functions put forth by Rolls and Grabenhorst (2008) and Schoenbaum and Esber (2010). They argue that the OFC facilitates decision-making based on preferences and stimulus-reinforcer associations, and when behavior depends on detailed, flexible and adjustable predictions of outcomes or on models of the reinforcement environment. Based on animal studies, Rushworth particularly emphasizes the role of the OFC in contrast to the anterior cingulate, arguing that the OFC is more involved in processing and selection of stimuli and their reward value, while the anterior cingulate focuses on the actions necessary to obtain those goals.

A similarity in most of these models of OMPFC functions is the important role of the OMPFC in monitoring. However, what is being monitored differs dramatically across models. The self-monitoring hypothesis focuses on monitoring of one's own behavior, while the models arising from the animal literature focus on monitoring of the environment for potential reinforcers, their associates and changes in reinforcement contingencies. In other words, the OMPFC monitors cues for reinforcers and outcomes rather than behavior. Rushworth et al. (2007), view this as a particularly crucial distinction, as they argue that the anterior cingulate has a primary function of monitoring actions and the outcomes of these actions, while the OMPFC focuses on the reward value of current or potential stimuli.

In considering the models based on stimulus-reward learning, it is important to note that these recent models do not posit a singular computational process is responsible for the OMPFC functions, but rather a set of processes are integrated within a larger framework related to valuation of expected outcomes. The potential ability of these recent models to provide a framework for explaining the seemingly heterogeneous group of behaviors and experimental results in OMPFC patients and animal paradigms suggest that a focus on the stimulus-reinforcer and goal valuation processes of the OMPFC may be particularly fruitful for developing a further understanding of the OMPFC. Care will be needed to develop this line of research with an eye to the specific computational processes that are dependent upon the OMPFC versus other connected brain regions. We note that there may be practical difficulties in developing clinical measures that directly test for abnormalities in the coding of valuation and changes in valuation in that it is not clear to what extent patients' declarative reports of valuation mirror or depend on the results of computations in the OMPFC. As elegantly described by Eslinger and Damasio (1985) and Damasio (1994), OMPFC patients may be able to express the risks (negative valuations) associated with behaviors, and yet nevertheless appear insensitive to these risks in their actual decision-making. Damasio (1996) attempts to explain this paradox with the somatic marker hypothesis, which proposes that the ability of autonomic signals to help guide decision-making is disrupted in these OMPFC patients. While it is clear that autonomic processes are not desiderata for coding changes in stimulus-reinforcer contingencies (Heims, Critchley, Dolan, Mathias, & Cipolotti, 2004), the idea that autonomic responses are integrated with other coding during decision-making may help explain the close proximity of areas related to autonomic processing to those involved in valuation processes.

10.2. Gaps in the literature

Given the important theoretical and conceptual strides arising from animal and neuroimaging studies, it is striking how few clinical tasks directly assess the valuation, integration and stimulus-reinforcer processes that lie at the heart of recent models of OMPFC functions. Some experimental neuropsychological studies, such as those conducted by Fellows and colleagues on preference judgments (Fellows & Farah, 2007) and the processing of negative feedback (i.e., errors; Wheeler & Fellows, 2008), have started to bridge the gap, but no such measures have been widely adopted to date. It is also striking how many of the behavioral domains that are captured in rating scales, such as emotional regulation and empathy, are not assessed by existing objective tasks. Similarly, despite compelling evidence for the autonomic functions of the ventromedial wall, measurement of autonomic functioning in the human clinical literature remains rare outside of few key paradigms (Naqvi, Tranel, & Bechara, 2006).

10.3. Diagnostic implications

Taken together, neuropsychological evaluation of the OMPFC remains an imperfect science. Traditional neuropsychological batteries, while useful in ruling out other potential pathologies, are

generally insensitive to lesions in this region. Evaluation of OFC and VMPFC dysfunction thus requires an integrative approach to the assessment, in which traditional neuropsychological batteries must be augmented or modified if they are to be sensitive to OFC or VMPFC dysfunction.

If, as we have argued, the range of deficits observed in OMPFC patients cannot be explained by a single unitary process, then no individual test is likely to serve as a gold standard for assessing OMPFC damage. Rather some combination of measures will be necessary to capture the different processes. Several different criteria should be considered in selecting measures of OMPFC functions, including the need to; (1) tap different functional domains, (2) tap domains with relevance to daily functioning, (3) tap different structural subregions and (4) the psychometric properties of the measures.

In terms of tapping different functional domains, we would suggest 5 domains warrant testing based on the strength of evidence that OMPFC damage disrupts such processes. These include: (1) the ability to change prepotent or previously acquired stimulus-reinforcer associations (e.g., OA and ORL, IGT); (2) olfactory processing (e.g., recognition/discrimination); (3) social processing (e.g., Faux Pas, emotional face recognition), (4) autobiographical memory, and (5) emotional characteristics of personality. For the sake of diagnostic utility in a protocol (and broad characterization of deficits), it will be more useful to include tasks that measure different domains rather than including measures that capture the same domain. Thus, for instance, given the apparent correlation between ORL and the IGT, the incremental utility of including both measures may be low relative to using two measures in different domains.

In clinical settings, the choice of OMPFC assessment measures may also be driven by the relationship of the functional domains to impairments in daily living. In these contexts, attention to the social impairments, and problems of emotional dysregulation or behavioral disinhibition may prove particularly critical. Such impairments have particular importance for treatment planning as some of these characteristics appear amenable to specific training programs (Solomon, Goodlin-Jones, & Anders, 2004) or behavioral modification strategies (Alderman, 2004). Thus, the benefits for treatment planning may accentuate the value of assessing social and emotional processing, even if such measures do not yet meet some of the remaining criteria.

As for testing different structural subregions, most of the human clinical literature does not allow for isolation of subregional impact on neuropsychological function. However, based on connectivity, functional neuroimaging, and electrophysiological studies, some degree of separation seems likely. For instance, olfactory processing is largely focused on the orbital surface. In contrast, autobiographical memory is likely to be more closely connected to the medial wall given the pattern of connections to the hippocampus and medial temporal cortical regions. Unfortunately, less clarity arises for other measures such as various personality-related changes where explicit experimental probes or preclinical literatures are lacking.

Because different forms of neuropathology produce different regional patterns of damage in the OMPFC, the type of pathology may impact test selection. For example the medial nature of Acom aneurysms suggests the importance of testing autobiographical memory (and memory in general) in such cases. The nature of the suspected pathology may also influence test selection due to the populations on which the measures have been developed or validated. For instance the Frontal Behavioral Inventory is particularly recommended in cases of FvFTD given that the scale was developed for and validated with FvFTD patients. In contrast, measures such as the FrSBe are not tied to a specific disease state and may as a result do better at detecting dysfunction in patients with other sources of OMPFC damage.

The final criterion is psychometric properties. Unfortunately, a major limitation of the experimental neuropsychological literature is the weak psychometric characterization and standardization of most of the measures that appear sensitive to OMPFC lesions. Indeed, other than UPSIT/SIT and a few of the rating scales, little normative data is available for most of the measures described above, and indeed many of the measures have not been standardized across labs. Accordingly, when taken in isolation, researchers and practitioners alike would be wise to apply appropriate levels of caution when using such measures to infer damage to the OFC or the VMPFC. At present, the lack of normative data for most of these experimental tasks and many of the behavioral scales is an impediment to their immediate adoption in clinical settings. The development of formalized and (age, gender, education) appropriately normed versions of these measures would be a welcome addition to the field.

The issue of specificity is particularly tricky in neuropsychology in that tasks often depend upon distributed networks of brain regions. Indeed, based on a network approach, we would expect damage to multiple areas to impact certain functions. For instance, the frequent common involvement of both dorsomedial (cingulate) areas and the OMFC in tasks requiring cognitive flexibility may reflect their closely linked circuitry (Price, 2006). In other words, truly high levels of specificity are unlikely for many cognitive tasks if comparisons are drawn with individuals with damage in other parts of functional networks. A clear example of this type of situation comes from patients with basal ganglia dysfunction. Disruption of normal basal ganglia functioning, either through lesions, or in disorders such as Parkinson's or Huntington's disease, disrupts frontal related functions (Stocchi & Brusa, 2000; Zgaljardic, Borod, Foldi, & Mattis, 2003), including alternation and reversal tasks (Hsieh, Chuang, Hwang, & Pai, 1998; Lawrence, Sahakian, Rogers, Hodges, & Robbins, 1999; Marie et al., 1999; Swainson et al., 2000). Because these effects likely occur through the dysfunction of the corticostriatal loops connecting the frontal cortex, striatum and thalamus (Alexander, DeLong, & Strick, 1986; Cummings, 1993), they do not challenge the hypothesis that impaired performance reflects disruption of OFC functioning. Indeed, depending upon the specific location of the basal ganglia disruption they may highlight the importance of OFC dysfunction in a task, even if the source of the dysfunction lies in the striatum rather than the OFC itself. Similar issues arise for the amygdala, whose input and interaction with the OMPFC appear essential for normal OMPFC functioning. Thus, it is no surprise that lesions affecting the amygdala often have impacts on tests that are sensitive to OMPFC lesions (e.g., Bar-On, Tranel, Denburg, & Bechara, 2003; Bechara, Damasio, Damasio, & Lee, 1999; Stone et al., 2003).

Given these network issues, a single test is probably unlikely to provide sufficient specificity when taken in isolation. However, when the full constellation of symptoms associated with OMPFC dysfunction emerge, the confidence in interpreting the data increases dramatically. It is hard to find explanations other than ventral frontal dysfunction in patients demonstrating acquired emotional dysregulation and social processing deficits if they also show deficits on a combination of experimental "OMPFC tasks" and olfactory recognition tasks, while showing relatively normal IQ.

11. Conclusions

In summary, we propose that research and clinical characterization of the OMPFC requires an integrative approach in which standard testing batteries are augmented with neuropsychiatric and frontal-specific rating scales in order to capture the full range of behavioral, cognitive and personality disturbance arising from OMPFC damage. While individual "OMPFC" measures are increas-

ingly utilized to assess the functioning of the OFC or VMPFC in psychiatric and neurological disorders, testing is often limited to just one or two measures. Given the heterogeneous nature of processes that appear to be subserved by the OMPFC, we suggest that a broader characterization is necessary to fully characterize OMPFC functioning. Both rating scales and olfactory recognition measures can be easily implemented in the clinical setting due to the presence of already existing normative data. Significant advantages may also come from integrating experimental tasks tapping responses to changing stimulus-reward contingencies, social processing and autobiographical memory, although the full potential of these measures will only be realized when researchers take up the challenge to develop standardized, well –normed versions of these measures. Such strides, when combined with advances in neuroimaging and neurophysiology have the potential to dramatically increase our understanding of the normal functioning of the OMPFC and the impact of dysfunction of the region on cognition and behavior.

References

Alderman, N. (2004). Disorders of behavior. In J. Ponsford (Ed.), *Cognitive and behavioral rehabilitation: From neurobiology to clinical practice* (pp. 269–298). New York: Guilford, New York.

Alexander, M. P., & Freedman, M. (1984). Amnesia after anterior communicating artery aneurysm rupture. *Neurology*, *34*, 752–757.

Alexander, G. E., DeLong, M. R., & Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual Review of Neuroscience*, *9*, 357–381.

Anderson, S. W., Damasio, H., Tranel, D., & Damasio, A. R. (1992). Cognitive sequelae of focal lesions in ventromedial frontal lobe. *Journal of Clinical and Experimental Neuropsychology*, *14*, 83.

Anderson, S. W., Barrash, J., Bechara, A., & Tranel, D. (2006). Impairments of emotion and real-world complex behavior following childhood- or adult-onset damage to ventromedial prefrontal cortex. *Journal of International Neuropsychological Society*, *12*, 224–235.

Angrilli, A., Palomba, D., Cantagallo, A., Maietti, A., & Stegagno, L. (1999). Emotional impairment after right orbitofrontal lesion in a patient without cognitive deficits. *Neuroreport*, *10*, 1741–1746.

Aron, A. R., & Poldrack, R. A. (2005). The cognitive neuroscience of response inhibition: Relevance for genetic research in attention-deficit/hyperactivity disorder. *Biological Psychiatry*, *57*, 1285–1292.

Barbas, H. (1988). Anatomic organization of basoventral and mediodorsal visual recipient prefrontal regions in the rhesus monkey. *Journal of Comparative Neurology*, *276*, 313–342.

Barbas, H., & Pandya, D. N. (1989). Architecture and intrinsic connections of the prefrontal cortex in the rhesus monkey. *Journal of Comparative Neurology*, *286*, 353–375.

Bar-On, R., Tranel, D., Denburg, N. L., & Bechara, A. (2003). Exploring the neurological substrate of emotional and social intelligence. *Brain*, *126*, 1790–1800.

Baron-Cohen, S., Jolliffe, T., Mortimore, C., & Robertson, M. (1997). Another advanced test of theory of mind: Evidence from very high functioning adults with autism or asperger syndrome. *Journal of Child Psychology and Psychiatry*, *38*, 813–822.

Barrash, J., & Anderson, S. W. (1993). *The Iowa rating scales of personality change*. Iowa City: University of Iowa, Department of Neurology.

Barrash, J., Tranel, D., & Anderson, S. W. (2000). Acquired personality disturbances associated with bilateral damage to the ventromedial prefrontal region. *Developmental Neuropsychology*, *18*, 355–381.

Bechara, A., Damasio, A. R., Damasio, H., & Anderson, S. W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition*, *50*, 7–15.

Bechara, A., Damasio, H., Tranel, D., & Anderson, S. W. (1998). Dissociation of working memory from decision making within the human prefrontal cortex. *Journal of Neuroscience*, *18*, 428–437.

Bechara, A., Damasio, H., Damasio, A. R., & Lee, G. P. (1999). Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making. *Journal of Neuroscience*, *19*, 5473–5481.

Beer, J. S., John, O. P., Scabini, D., & Knight, R. T. (2006). Orbitofrontal cortex and social behavior: Integrating self-monitoring and emotion-cognition interactions. *Journal of Cognitive Neuroscience*, *18*, 871–879.

Berlin, H. A., Rolls, E. T., & Kischka, U. (2004). Impulsivity, time perception, emotion and reinforcement sensitivity in patients with orbitofrontal cortex lesions. *Brain*, *127*, 1108–1126.

Black, D. N., Stip, E., Bedard, M., Kabay, M., Paquette, I., & Bigras, M. J. (2000). Leukotomy revisited: Late cognitive and behavioral effects in chronic institutionalized schizophrenics. *Schizophrenia Research*, *43*, 57–64.

Blair, R. J., & Cipolotti, L. (2000). Impaired social response reversal. A case of "acquired sociopathy.". *Brain*, *123*, 1122–1141.

Bottger, S., Prosiegel, M., Steiger, H. J., & Yassouridis, A. (1998). Neurobehavioural disturbances, rehabilitation outcome, and lesion site in patients after rupture and repair of anterior communicating artery aneurysm. *Journal of Neurolology, Neurosurgery, and Psychiatry*, *65*, 93–102.

Brand, M., & Markowitsch, H. J. (2006). Memory processes and the orbitofrontal cortex. In D. H. Zald, & S. L. Rauch (Eds.), *The orbitofrontal cortex* (pp. 285–306). Oxford, UK: Oxford University Press.

Brutkowski, S., & Davrowska, J. (1963). Disinhibition after prefrontal lesions as a function of duration of intertrial intervals. *Science*, *139*, 505–506.

Butter, C. M. (1969). Perseveration in extinction and in discrimination reversal tasks following selective frontal ablations in Macaca mulatta. *Physiology and Behavior*, *4*, 163–171.

Butters, N., & Pandya, D. N. (1969). Retention of delayed-alternation: Effect of selective lesions of the sulcus pricipalis. *Science*, *165*, 1271–1273.

Butters, N., Butter, C., Rosen, J., & Stein, D. (1973). Behavioral effects of sequential and one-stage ablations of orbital prefrontal cortex in the monkey. *Experimental Neurology*, *39*, 204–214.

Carmichael, S. T., & Price, J. L. (1996). Connectional networks within the orbital and medial prefrontal cortex of macaque monkeys. *Journal of Comparative Neurology*, *346*, 179–207.

Carmichael, S. T., Clugnet, M. C., & Price, J. L. (1994). Central olfactory connections in the macaque monkey. *Journal of Comparative Neurology*, *346*, 403–434.

Chase, H. W., Clark, L., Myers, C. E., Gluck, M. A., Sahakian, B. J., Bullmore, E. T., et al. (2008). The role of the orbitofrontal cortex in human discrimination learning. *Neuropsychologia*, *46*, 1326–1337.

Clark, L., Manes, F., Nagui, A., Sahakian, B. J., & Robbins, T. W. (2003). The contributions of lesion laterality and lesion volume to decision-making impairment following frontal lobe damage. *Neuropsychologia*, *41*, 1474–1483.

Clark, L., Bechara, A., Damasio, H., Aitken, M. R., Sahakian, B. J., & Robbins, T. W. (2008). Differential effects of insular and ventromedial prefrontal cortex lesions on risky decision-making. *Brain*, *131*, 1311–1322.

Cools, R., Clark, L., Owen, A. M., & Robbins, T. W. (2002). Defining the neural mechanisms of probabilistic reversal learning using event-related functional magnetic resonance imaging. *Journal of Neuroscience*, *22*, 4563–4567.

Courville, C. B. (1937). *Pathology of the central nervous system; a study based upon a survey of lesions found in a series of 15,000 autopsies*. Oxford, UK: Pacific Press Publishing Association.

Cummings, J. L. (1993). Frontal-subcortical circuits and human behavior. *Archives of Neurology*, *50*, 873–880.

Cummings, J. L., Mega, M., Gray, K., Rosenberg-Thompson, S., Carusi, D. A., & Gornbein, J. (1994). The neuropsychiatric inventory: Comprehensive assessment of psychopathology in dementia. *Neurology*, *44*, 2308–2314.

Curtis, C. E., Zald, D. H., Lee, J. T., & Pardo, J. V. (2000). Object and spatial alternation tasks with minimal delays activate the right anterior hippocampus proper in humans. *Neuroreport*, *11*, 2203–2207.

Damasio, A. R. (1994). *Descartes' error: Emotion, rationality and the human brain*. New York: GP Putnam.

Damasio, A. R. (1996). The somatic marker hypothesis and the possible functions of the prefrontal cortex. *Philosophical Transactions of the Royal Society of London - Series B: Biological Sciences*, *351*, 1413–1420.

DeLuca, J. (1993). Predicting neurobehavioral patterns following anterior Communicating Artery Aneurysm. *Cortex*, *29*, 639–647.

DeLuca, J., & Diamond, B. J. (1995). Aneurysm of the anterior communicating artery—A review of neuroanatomical and neuropsychological sequelae. *Journal of Clinical and Experimental Neuropsychology*, *17*, 100–121.

Dias, R., Robbins, T. W., & Roberts, A. C. (1996). Dissociation in prefrontal cortex of affective and attentional shifts. *Nature*, *380*, 69–72.

Dias, R., Robbins, T. W., & Roberts, A. C. (1997). Dissociable forms of inhibitory control within prefrontal cortex with an analog of the Wisconsin Card Sort Test: Restriction to novel situations and independence from "on-line" processing. *Journal of Neuroscience*, *17*, 9285–9297.

Doty, R. L., Shaman, P., Kimmelman, C. P., & Dann, M. S. (1984). University of Pennsylvania Smell Identification Test: A rapid quantitative olfactory function test for the clinic. *Laryngoscope*, *94*, 176–178.

Doty, R. L., Li, C., Mannon, L. J., & Yousem, D. M. (1998). Olfactory dysfunction in multiple sclerosis: Relation to plaque load in inferior frontal and temporal lobes. *Annals of the New York Academy of Sciences*, *855*, 781–786.

Doty, R. L., Li, C., Mannon, L. J., & Yousem, D. M. (1999). Olfactory dysfunction in multiple sclerosis: Relation to longitudinal changes in plaque numbers in central olfactory structures. *Neurology*, *53*, 880–882.

Dougherty, D., Shin, L., & Rauch, S. L. (2006). Orbitofrontal cortex activation during functional neuroimaging studies of emotion induction in humans. In D. H. Zald, & S. L. Rauch (Eds.), *Orbitofrontal cortex* (pp. 377–392). Oxford, U.K.: Oxford University Press.

Drewe, E. A. (1975). Go–no go learning after frontal lobe lesions in humans. *Cortex*, *11*, 8–16.

Elliott, R., & Dolan, R. J. (1999). Differential neural responses during performance of matching and nonmatching to sample tasks at two delay intervals. *Journal of Neuroscience*, *19*, 5066–5073.

Ernst, M., Grant, S. J., London, E. D., Contoreggi, C. S., Kimes, A. S., & Spurgeon, L. (2003). Decision making in adolescents with behavior disorders and adults with substance abuse. *American Journal of Psychiatry*, *160*, 33–40.

Eslinger, P. J., & Damasio, A. R. (1985). Severe disturbance of higher cognition after bilateral frontal-lobe ablation–patient EVR. *Neurology*, *35*, 1731–1741.

Farrow, T. F., Zheng, Y., Wilkinson, I. D., Spence, S. A., Deakin, J. F., Tarrier, N., et al. (2001). Investigating the functional anatomy of empathy and forgiveness. *Neuroreport*, *12*, 2433–2438.

Fecteau, S., Knoch, D., Fregni, F., Sultani, N., Boggio, P., & Pascual-Leone, A. (2007). Diminishing risk-taking behavior by modulating activity in the prefrontal cortex: A direct current stimulation study. *Journal of Neuroscience*, *27*, 12500–12505.

Fecteau, S., Pascual-Leone, A., Zald, D. H., Liguori, P., Theoret, H., Boggio, P. S., et al. (2007). Activation of prefrontal cortex by transcranial direct current stimulation reduces appetite for risk during ambiguous decision making. *Journal of Neuroscience*, *27*, 6212–6218.

Fellows, L. K., & Farah, M. J. (2003). Ventromedial frontal cortex mediates affective shifting in humans: Evidence from a reversal learning paradigm. *Brain*, *126*, 1830–1837.

Fellows, L. K., & Farah, M. J. (2005). Different underlying impairments in decision-making following ventromedial and dorsolateral frontal lobe damage in humans. *Cerebral Cortex*, *15*(1), 58–63.

Fellows, L. K., & Farah, M. J. (2007). The role of ventromedial prefrontal cortex in decision making: Judgment under uncertainty or judgment per se? *Cerebral Cortex*, *17*, 2669–2674.

Fernandez-Duque, D., & Black, S. E. (2005). Impaired recognition of negative facial emotions in patients with frontotemporal dementia. *Neuropsychologia*, *43*, 1673–1687.

Floden, D., Alexander, M. P., Kubu, C. S., Katz, D., & Stuss, D. T. (2008). Impulsivity and risk-taking behavior in focal frontal lobe lesions. *Neuropsychologia*, *46*, 213–223.

Franceschi, M., Anchisi, D., Pelati, O., Zuffi, M., Matarrese, M., Moresco, R. M., et al. (2005). Glucose metabolism and serotonin receptors in the frontotemporal lobe degeneration. *Annals of Neurology*, *57*, 216–225.

Freedman, M., & Oscar-Berman, M. (1986). Bilateral frontal lobe disease and selective delayed response deficits in humans. *Behavioral and Neural Biology*, *100*, 337–342.

Freedman, M., Black, S., Ebert, P., & Binns, M. (1998). Orbitofrontal function, object alternation and perseveration. *Cerebral Cortex*, *8*, 18–27.

Fujii, T., Suzuki, M., Okuda, J., Ohtake, H., Tanji, K., Yamaguchi, K., et al. (2004). Neural correlates of context memory with real-world events. *Neuroimage*, *21*, 1596–1603.

Fujiwara, E., Schwartz, M. L., Gao, F. S., Black, R. E., & Levine, B. (2008). Ventral frontal cortex functions and quantified MRI in traumatic brain injury. *Neuropsychologia*, *46*, 461–474.

Fukui, H., Murai, T., Fukuyama, H., Hayashi, T., & Hanakawa, T. (2005). Functional activity related to risk anticipation during performance of the Iowa Gambling Task. *NeuroImage*, *24*, 253–259.

Gallagher, H. L., & Frith, C. D. (2003). Functional imaging of 'theory of mind'. *Trends in Cognitive Sciences*, *7*, 77–83.

Gazzeri, R., Galarza, M., & Gazzeri, G. (2008). Giant olfactory groove meningioma: Ophthalmological and cognitive outcome after bifrontal microsurgical approach. *Acta Neurochirurgia*, *150*, 1117–1125.

Godefroy, O., & Rousseaux, M. (1996). Divided and focused attention in patients with lesion of the prefrontal cortex. *Brain and Cognition*, *30*, 155–174.

Goldman, P. S., Rosvold, H. E., Vest, B., & Galkin, T. W. (1971). Analysis of the delayed-alternation deficit produced by dorsolateral prefrontal lesions in the rhesus monkey. *Journal of Comparative and Physiological Psychology*, *77*, 212–220.

Gottfried, J. A., & Zald, D. H. (2005). On the scent of human olfactory orbitofrontal cortex: Meta-analysis and comparison to non-human primates. *Brain Research Reviews*, *50*, 287–304.

Gottfried, J., Small, D., & Zald, D. H. (2006). The chemical senses. In D. H. Zald, & S. L. Rauch (Eds.), *Orbitofrontal cortex* (pp. 125–172). Oxford, U.K.: Oxford University Press.

Grace, J., & Malloy, P. F. (2001). *Frontal systems behavior scale: Professional manual*. Lutz, Florida: Psychological Assessment Resources.

Grace, J., Stout, J. C., & Malloy, P. F. (1999). Assessing frontal lobe behavioral syndromes with the Frontal Lobe Personality Scale. *Assessment*, *6*, 269–284.

Gregory, C., Lough, S., Stone, V., Erzinclioglu, S., Martin, L., Baron-Cohen, S., et al. (2002). Theory of mind in patients with frontal variant frontotemporal dementia and Alzheimer's disease: Theoretical and practical implications. *Brain*, *125*, 752–764.

Harlow, J. M. (1868). Recovery from the passage of an iron bar through the head. *Publication Massachusetts Medical Society*, *2*, 327–346.

Heberlein, A. S., Padon, A. A., Gillihan, S. J., Farah, M. J., & Fellows, L. K. (2008). Ventromedial frontal lobe plays a critical role in facial emotion recognition. *Journal of Cognitive Neuroscience*, *20*, 721–733.

Heims, H. C., Critchley, H. D., Dolan, R., Mathias, C. J., & Cipolotti, L. (2004). Social and motivational functioning is not critically dependent on feedback of autonomic responses: Neuropsychological evidence from patients with pure autonomic failure. *Neuropsychologia*, *42*, 1979–1988.

Hooker, C. I., & Knight, R. T. (2006). The role of the lateral orbitofrontal cortex in the inhibitory control of emotion. In D. Zald, & S. Rauch (Eds.), *The orbitofrontal cortex* (pp. 307–324). Oxford, U.K.: Oxford University Press.

Hornak, J., Rolls, E. T., & Wade, D. (1996). Face and voice expression identification in patients with emotional and behavioural changes following ventral frontal lobe damage. *Neuropsychologia*, *34*, 247–261.

Hornak, J., Bramham, J., Rolls, E. T., Morris, R. G., O'Doherty, J., Bullock, P. R., et al. (2003). Changes in emotion after circumscribed surgical lesions of the orbitofrontal and cingulate cortices. *Brain*, *126*, 1691–1712.

Hornak, J., O'Doherty, J., Bramham, J., Rolls, E. T., Morris, R. G., Bullock, P. R., et al. (2004). Reward-related reversal learning after surgical excisions in orbito-frontal or dorsolateral prefrontal cortex in humans. *Journal of Cognitive Neuroscience*, *16*, 463–478.

Hsieh, S., Chuang, Y. Y., Hwang, W. J., & Pai, M. C. (1998). A specific shifting deficit in Parkinson's disease: A reversal shift of consistent stimulus-response mappings. *Perceptual and Motor Skills*, *87*, 1107–1119.

Hulshoff Pol, H. E., Hijman, R., Tulleken, C. A., Heeren, T. J., Schneider, N., & van Ree, J. M. (2002). Odor discrimination in patients with frontal lobe damage and Korsakoff's syndrome. *Neuropsychologia*, *40*, 888–891.

Hynes, C. A., Baird, A. A., & Grafton, S. T. (2006). Differential role of the orbital frontal lobe in emotional versus cognitive perspective-taking. *Neuropsychologia*, *44*, 374–383.

Iversen, S., & Mishkin, M. (1970). Perseverative interference in monkeys following selective lesions of the inferior prefrontal convexity. *Experimental Brain Research*, *11*, 376–386.

Izquierdo, A., Suda, R. K., & Murray, E. A. (2004). Bilateral orbital prefrontal cortex lesions in rhesus monkeys disrupt choices guided by both reward value and reward contingency. *Journal of Neuroscience*, *24*, 7540–7548.

Jones-Gotman, M., & Zatorre, R. J. (1988). Olfactory identification deficits in patients with focal cerebral excision. *Neuropschologia*, *26*, 387–400.

Kazama, A., & Bachevalier, J. (2009). Selective aspiration or neurotoxic lesions of orbital frontal areas 11 and 13 spared monkeys' performance on the object discrimination reversal task. *Journal of Neuroscience*, *29*, 2794–2804.

Keane, J., Calder, A. J., Hodges, J. R., & Young, A. W. (2002). Face and emotion processing in frontal variant frontotemporal dementia. *Neuropsychologia*, *40*, 655–665.

Kertesz, A., Davidson, W., & Fox, H. (1997). Frontal behavioral inventory: Diagnostic criteria for frontal lobe dementia. *Canadian Journal of Neurological Sciences*, *24*, 29–36.

Knoch, D., Treyer, V., Regard, M., Muri, R. M., Buck, A., & Weber, B. (2006). Lateralized and frequency-dependent effects of prefrontal rTMS on regional cerebral blood flow. *Neuroimage*, *31*, 641–648.

Kringelbach, M. L., & Rolls, E. T. (2003). Neural correlates of rapid reversal learning in a simple model of human social interaction. *Neuroimage*, *20*, 1371–1383.

Kuhnen, C. M., & Knutson, B. (2005). The neural basis of financial risk taking. *Neuron*, *47*, 763–770.

Lamm, C., Nusbaum, H. C., Meltzoff, A. N., & Decety, J. (2007). What are you feeling? Using functional magnetic resonance imaging to assess the modulation of sensory and affective responses during empathy for pain. *PLoS One*, *2*, e1292.

Lavenu, I., & Pasquier, F. (2005). Perception of emotion on faces in frontotemporal dementia and Alzheimer's disease: A longitudinal study. *Dementia and Geriatric Cognitive Disorders*, *19*, 37–41.

Lavenu, I., Pasquier, F., Lebert, F., Petit, H., & Van der, L. M. (1999). Perception of emotion in frontotemporal dementia and Alzheimer disease. *Alzheimer Disease and Associated Disorder*, *13*, 96–101.

Lawrence, A. D., Sahakian, B. J., Rogers, R. D., Hodges, J. R., & Robbins, T. W. (1999). Discrimination, reversal, and shift learning in Huntington's disease: Mechanisms of impaired response selection. *Neuropsychologia*, *37*, 1359–1374.

Leimkuhler, M. E., & Mesulam, M. M. (1985). Reversible go–no go deficits in a case of frontal lobe tumor. *Annals of Neurology*, *18*, 617–619.

Levine, B. (2004). Autobiographical memory and the self in time: Brain lesion effects, functional neuroanatomy, and lifespan development. *Brain & Cognition*, *55*, 54–68.

Levine, B., Svoboda, E., Hay, J. F., Winocur, G., & Moscovitch, M. (2002). Aging and autobiographical memory: Dissociating episodic from semantic retrieval. *Psychology and Aging*, *17*, 677–689.

Levine, B., Black, S. E., Cheung, G., Campbell, A., O'Toole, C. O., & Schwartz, M. L. (2005). Gambling task performance in traumatic brain injury: Relationships to injury severity, atrophy, lesion location, and cognitive and psychosocial outcome. *Cognitive Behavioral Neurology*, *18*, 45–54.

Levine, B., Kovacevic, N., Nica, E. I., Cheung, G., Gao, F., Schwartz, M. L., et al. (2008). The Toronto traumatic brain injury study: Injury severity and quantified MRI. *Neurology*, *70*, 771–778.

Lough, S., Kipps, C. M., Treise, C., Watson, P., Blair, J. R., & Hodges, J. R. (2006). Social reasoning, emotion and empathy in frontotemporal dementia. *Neuropsychologia*, *44*, 950–958.

Lu, P. H., & Cummings, J. L. (2006). Frontotemporal dementia and the orbitofrontal cortex. In D. H. Zald, & S. L. Rauch (Eds.), *Orbitofrontal cortex*. Oxford, U.K.: Oxford University Press.

Luzzi, S., Snowden, J. S., Neary, D., Coccia, M., Provinciali, L., & Lambon Ralph, M. A. (2007). Distinct patterns of olfactory impairment in Alzheimer's disease, semantic dementia, frontotemporal dementia, and corticobasal degeneration. *Neuropsychologia*, *45*, 1823–1831.

Malloy, P., Tremont, G., Grace, J., & Frakey, L. (2007). The frontal systems behavior scale discriminates frontotemporal dementia from Alzheimer's disease. *Alzheimer's and Dementia*, *3*, 200–203.

Manes, F., Sahakian, B., Clark, L., Rogers, R., Antoun, N., Aitken, M., et al. (2002). Decision-making processes following damage to the prefrontal cortex. *Brain*, *125*, 624–639.

Marie, R. M., Barre, L., Dupuy, B., Viader, F., Defer, G., & Baron, J. C. (1999). Relationships between striatal dopamine denervation and frontal executive tests in Parkinson's disease. *Neuroscience Letters*, *260*, 77–80.

Marinkovic, K., Trebon, P., Chauvel, P., & Halgren, E. (2000). Localized face processing by the human prefrontal cortex: Face-selective intracerebral potentials and post-lesiondeficits. *Cognitive Neuropsychology*, *17*, 187–199.

Martin, G. E., Junque, C., Juncadella, M., Gabarros, A., de Miquel, M. A., & Rubio, F. (2009). Olfactory dysfunction after subarachnoid hemorrhage caused by ruptured aneurysms of the anterior communicating artery. *Journal of Neurosurgery*, *111*, 958–962.

Mavaddat, N., Kirkpatrick, P. J., Rogers, R. D., & Sahakian, B. J. (2000). Deficits in decision-making in patients with aneurysms of the anterior communicating artery. *Brain*, *123*, 2109–2117.

McKinnon, M. C., Nica, E. I., Sengdy, P., Kovacevic, N., Moscovitch, M., Freedman, M., et al. (2008). Autobiographical memory and patterns of brain atrophy in frontotemporal lobar degeneration. *Journal of Cognitive Neuroscience*, *20*, 1839–1853.

Meunier, M., Bachevalier, J., & Mishkin, M. (1997). Effects of orbital frontal and anterior cingulate lesions on object and spatial memory in rhesus monkeys. *Neuropsychologia*, *35*, 999–1015.

Mishkin, M. (1957). Effects of small frontal lesions on delayed alternation in monkeys. *Journal of Neurophysiology*, *20*, 615–622.

Mishkin, M. M. (1964). Preservation of central sets after frontal lesions in monkeys. In J. M. Warren, & K. Akert (Eds.), *The frontal granular cortex and behavior* (pp. 219–241). New York: McGraw-Hill.

Mishkin, M., & Manning, F. J. (1978). Non-spatial memory after selective prefrontal lesions in monkeys. *Brain Research*, *143*, 313–323.

Mishkin, M., Vest, B., Waxler, M., & Rosvold, H. E. (1969). A re-examination of the effects of frontal lesions on object alternation. *Neuropsychologia*, *7*, 357–363.

Mobbs, D., Petrovic, P., Marchant, J. L., Hassabis, D., Weiskopf, N., Seymour, B., et al. (2007). When fear is near: Threat imminence elicits prefrontal-periaqueductal gray shifts in humans. *Science*, *317*, 1079–1083.

Naqvi, N., Tranel, D., & Bechara, A. (2006). Visceral and decision-making functions of the ventromedial prefrontal cortex. In D. H. Zald, & S. L. Rauch (Eds.), *Orbitofrontal cortex*. Oxford, U.K.: Oxford University Press.

O'Doherty, J., & Dolan, R. (2006). The role of human orbitofrontal cortex in reward prediction and behavioral choice: Insights from neuroimaging. In D. H. Zald, & S. L. Rauch (Eds.), *The orbitofrontal cortex* (pp. 264–284). Oxford U.K.: Oxford University Press.

O'Doherty, J., Critchley, H., Deichmann, R., & Dolan, R. J. (2003). Dissociating valence of outcome from behavioral control in human orbital and ventral prefrontal cortices. *Journal of Neuroscience*, *23*, 7931–7939.

Pang, D. (1989). Physics and pathology of closed head injury. In M. Lezak & A. R. Liss (Eds.), *Assessment of the behavioral consequences of head trauma* (pp. 1–17), New York.

Pardini, M., Huey, E. D., Cavanagh, A. L., & Grafman, J. (2009). Olfactory function in corticobasal syndrome and frontotemporal dementia. *Archives of Neurolology*, *66*, 92–96.

Parizel, P. M., Ozsarlak, Van Goethem, J. W., van den, H. L., Dillen, C., Verlooy, J., et al. (1998). Imaging findings in diffuse axonal injury after closed head trauma. *European Journal of Radiology*, *8*, 960–965.

Passingham, R. (1975). Delayed matching after selective prefrontal lesions in monkeys (*Macaca mulatta*). *Brain Research*, *92*, 89–102.

Paulus, M. P., Rogalsky, C., Simmons, A., Feinstein, J. S., & Stein, M. B. (2003). Increased activation in the right insula during risk-taking decision making is related to harm avoidance and neuroticism. *Neuroimage*, *19*, 1439–1448.

Peters, J., & Buchel, C. (2010). Neural representations of subjective reward value. *Behavioral Brain Research*, *213*, 135–141.

Picton, T. W., Stuss, D. T., Alexander, M. P., Shallice, T., Binns, M. A., & Gillingham, S. (2007). Effects of focal frontal lesions on response inhibition. *Cerebral Cortex*, *17*, 826–838.

Plaisted, K. C., & Sahakian, B. J. (1997). Dementia of frontal lobe type-living in the here and now. *Aging and Mental Health*, *1*, 293–295.

Potter, H., & Butters, N. (1980). An assessment of olfactory deficits in patients with damage to prefrontal cortex. *Neuropsychologia*, *18*, 621–628.

Pribram, K. H., & Mishkin, M. (1956). Analysis of the effects of frontal lesions in monkey: III. Object alternation. *Journal of Comparative and Physiological Psychology*, *49*, 41–45.

Price, J. L. (2006). Connections of the orbital cortex. In D. H. Zald, & S. L. Rauch (Eds.), *Orbitofrontal cortex* (pp. 39–56). Oxford, UK: Oxford University Press.

Prigatano, G. P. (1991). Disturbances of self-awareness of deficit after traumatic brain Injury. In G. P. Prigatano, & D. L. Schacter (Eds.), *Awareness of deficit after brain injury: clinical and theoretical issues*. New York: Oxford University Press, pp. 111–126.

Rahman, S., Robbins, T. W., & Sahakian, B. J. (1999). Comparative cognitive neuropsychological studies of frontal lobe function: Implications for therapeutic strategies in frontal variant frontotemporal dementia. *Dementia and Geriatric Cognitive Disorders*, *10*, 15–28.

Rankin, K. P., Kramer, J. H., & Miller, B. L. (2005). Patterns of cognitive and emotional empathy in frontotemporal lobar degeneration. *Cognitive and Behavioral Neurology*, *18*, 28–36.

Remijnse, P. L., Nielen, M. M. A., Uylings, H. B. M., & Veltman, D. J. (2005). Neural correlates of a reversal learning task with an affectively neutral baseline: An event-related fMRI study. *NeuroImage*, *26*, 609–618.

Roesch, M., & Schoenbaum, G. (2006). From associations to expectancies: orbitofrontal cortex as gateway between the limbic system and representational memory. In D. H. Zald, & S. L. Rauch (Eds.), *The orbitofrontal cortex*. Oxford, U.K: University Press, pp. 199–236.

Rogers, R. D., Everitt, B. J., Baldacchino, A., Blackshaw, A. J., Swainson, R., Wynne, K., et al. (1999). Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan-depleted normal volunteers: Evidence for monoaminergic mechanisms. *Neuropsychopharmacology*, *20*, 322–339.

Rolls, E. T. (2004). The functions of the orbitofrontal cortex. *Brain & Cognition*, *55*, 11–29.

Rolls, E. T. (2006). The neurophysiology and functions of the orbitofrontal cortex. In D. H. Zald, & S. L. Rauch (Eds.), *The orbitofrontal cortex*. Oxford, U.K.: Oxford University Press, pp. 95–124.

Rolls, E. T., & Grabenhorst, F. (2008). The orbitofrontal cortex and beyond: From affect to decision-making. *Progress in Neurobiology*, *86*, 216–244.

Rolls, E. T., Hornak, J., Wade, D., & McGrath, J. (1994). Emotion-related learning in patients with social and emotional changes associated with frontal lobe damage. *Journal of Neurology, Neurosurgery and Psychiatry*, *57*, 1518–1524.

Rosen, H. J., Pace-Savitsky, K., Perry, R. J., Kramer, J. H., Miller, B. L., & Levenson, R. W. (2004). Recognition of emotion in the frontal and temporal variants of frontotemporal dementia. *Dementia and Geriatric Cognitive Disorders*, *17*, 277–281.

Rowe, A. D., Bullock, P. R., Polkey, C. E., & Morris, R. G. (2001). "Theory of mind" impairments and their relationship to executive functioning following frontal lobe excisions. *Brain*, *124*, 600–616.

Rudebeck, P. H., & Murray, E. A. (2008). Amygdala and orbitofrontal cortex lesions differentially influence choices during object reversal learning. *Journal of Neuroscience*, *28*, 8338–8343.

Rushworth, M. F., Behrens, T. E., Rudebeck, P. H., & Walton, M. E. (2007). Contrasting roles for cingulate and orbitofrontal cortex in decisions and social behaviour. *Trends in Cognitive Sciences*, *11*, 168–176.

Sabbagh, M. A., Moulson, M. C., & Harkness, K. L. (2004). Neural correlates of mental state decoding in human adults: An event-related potential study. *Journal of Cognitive Neuroscience*, *16*, 415–426.

Salmaso, D., & Denes, G. (1982). Role of the frontal lobes on an attention task: A signal detection analysis. *Perceptual and Motor Skills*, *54*, 1147–1150.

Schoenbaum, G., & Esber, G. R. (2010). How do you (estimate you will) like them apples? Integration as a defining trait of orbitofrontal function. *Current Opinion in Neurobiology*, *20*, 205–211.

Schultz, W., & Tremblay, L. (2006). Involvement of primate orbitofrontal neurons in reward, uncertainty and learning. In D. H. Zald, & S. L. Rauch (Eds.), *Orbitofrontal cortex* (pp. 173–198). Oxford, U.K.: Oxford University Press.

Shamay, S. G., Tomer, R., & Aharon-Peretz, J. (2002). Deficit in understanding sarcasm in patients with prefronal lesion is related to impaired empathic ability. *Brain and Cognition*, *48*, 558–563.

Shamay-Tsoory, S. G., & Aharon-Peretz, J. (2007). Dissociable prefrontal networks for cognitive and affective theory of mind: A lesion study. *Neuropsychologia*, *45*, 3054–3067.

Shamay-Tsoory, S. G., Tomer, R., Goldsher, D., Berger, B. D., & Aharon-Peretz, J. (2004). Impairment in cognitive and affective empathy in patients with brain lesions: Anatomical and cognitive correlates. *Journal of Clinical and Experimental Neuropsychology*, *26*, 1113–1127.

Shamay-Tsoory, S. G., Tomer, R., Berger, B. D., & Aharon-Peretz, J. (2003). Characterization of empathy deficits following prefrontal brain damage: The role of the right ventromedial prefrontal cortex. *Journal of Cognitive Neuroscience*, *15*, 324–337.

Shamay-Tsoory, S. G., Tomer, R., & Aharon-Peretz, J. (2005). The neuroanatomical basis of understanding sarcasm and its relationship to social cognition. *Neuropsychology*, *19*, 288–300.

Shamay-Tsoory, S. G., Tomer, R., Berger, B. D., Goldsher, D., & Aharon-Peretz, J. (2005). Impaired "affective theory of mind" is associated with right ventromedial prefrontal damage. *Cognitive and Behavioral Neurology*, *18*, 55–67.

Shamay-Tsoory, S. G., Aharon-Peretz, J., & Perry, D. (2009). Two systems for empathy: A double dissociation between emotional and cognitive empathy in inferior frontal gyrus versus ventromedial prefrontal lesions. *Brain*, *132*, 617–627.

Simmonds, D. J., Pekar, J. J., & Mostofsky, S. H. (2008). Meta-analysis of Go/No-go tasks demonstrating that fMRI activation associated with response inhibition is task-dependent. *Neuropsychologia*, *46*, 224–232.

Slachevsky, A., Villalpando, J. M., Sarazin, M., Hahn-Barma, V., Pillon, B., & Dubois, B. (2004). Frontal assessment battery and differential diagnosis of frontotemporal dementia and Alzheimer disease. *Archives of Neurology*, *61*, 1104–1107.

Solomon, M., Goodlin-Jones, B. L., & Anders, T. F. (2004). A social adjustment enhancement intervention for high functioning autism, Asperger's syndrome, and pervasive developmental disorder NOS. *Journal of Autism and Developmental Disorders*, *34*, 649–656.

Spinella, M. (2002). Correlations among behavioral measures of orbitofrontal function. *International Journal of Neuroscience*, *112*, 1359–1369.

Stocchi, F., & Brusa, L. (2000). Cognition and emotion in different stages and subtypes of Parkinson's disease. *Journal of Neurology*, *247*(Suppl. 2), II114–II121.

Stone, V. E., Baron-Cohen, S., & Knight, R. T. (1998). Frontal lobe contributions to theory of mind. *Journal of Cognitive Neuroscience*, *10*, 640–656.

Stone, V. E., Baron-Cohen, S., Calder, A., Keane, J., & Young, A. (2003). Acquired theory of mind impairments in individuals with bilateral amygdala lesions. *Neuropsychologia*, *41*, 209–220.

Stuss, D. T., Kaplan, E. F., Benson, D. F., Weir, W. S., Chiulli, S., & Sarazin, F. F. (1982). Evidence for the involvement of orbitofrontal cortex in memory functions: An interference effect. *Journal of Comparative and Physiological Psychology*, *96*, 913–925.

Stuss, D. T., & Benson, D. F. (1984). Neuropsychological studies of the frontal lobes. *Psychological Bulletin*, *95*, 3–28.

Stuss, D. T., Benson, D. F., Kaplan, E. F., Weir, W. S., Naeser, M. A., Lieberman, I., et al. (1983). The involvement of orbitofrontal cerebrum in cognitive tasks. *Neuropsychologia*, *21*, 235–248.

Stuss, D. T., Levine, B., Alexander, M. P., Hong, J., Palumbo, C., Hamer, L., et al. (2000). Wisconsin Card Sorting Test performance in patients with focal frontal and posterior brain damage: Effects of lesion location and test structure on separable cognitive processes. *Neuropsychologia*, *38*, 388–402.

Stuss, D. T., Gallup, G. G., Jr., & Alexander, M. P. (2001). The frontal lobes are necessary for 'theory of mind'. *Brain*, *124*, 279–286.

Stuss, D. T. (1991). Self, awareness, and the frontal lobes: a neuropsychologicalperspective. In J. Strauss, & G. R. Goethals (Eds.), *The self: Interdisciplinary approaches*. New York: Springer-Verlag, pp. 255–277.

Svoboda, E., McKinnon, M. C., & Levine, B. (2006). The functional neuroanatomy of autobiographical memory: A meta-analysis. *Neuropsychologia*, *44*, 2189–2208.

Swainson, R., Rogers, R. D., Sahakian, B. J., Summers, B. A., Polkey, C. E., & Robbins, T. W. (2000). Probabilistic learning and reversal deficits in patients with Parkinson's disease or frontal or temporal lobe lesions: Possible adverse effects of dopaminergic medication. *Neuropsychologia*, *38*, 596–612.

Swick, D., Ashley, V., & Turken, A. U. (2008). Left inferior frontal gyrus is critical for response inhibition. *BMC Neuroscience*, *9*, 102.

Tatu, L., Moulin, T., Bogousslavsky, J., & Duvernoy, H. (1998). Arterial territories of the human brain: Cerebral hemispheres. *Neurology*, *50*, 1699–1708.

Tobler, P. N., O'Doherty, J. P., Dolan, R. J., & Schultz, W. (2007). Reward value coding distinct from risk attitude-related uncertainty coding in human reward systems. *Journal of Neurophysiology*, *97*, 1621–1632.

Torralva, T., Kipps, C. M., Hodges, J. R., Clark, L., Bekinschtein, T., Roca, M., et al. (2007). The relationship between affective decision-making and theory of mind in the frontal variant of fronto-temporal dementia. *Neuropsychologia*, *45*, 342–349.

Torralva, T., Roca, M., Gleichgerrcht, E., Bekinschtein, T., & Manes, F. (2009). A neuropsychological battery to detect specific executive and social cognitive impairments in early frontotemporal dementia. *Brain*, *132*, 1299–1309.

Tranel, D., Bechara, A., & Denburg, N. L. (2002). Asymmetric functional roles of right and left ventromedial prefrontal cortices in social conduct, decision-making, and emotional processing. *Cortex*, *38*, 589–612.

Turner, G., & Levine, B. (2006). The functional neuroanatomy of classic delayed response tasks in humans and the limitations of cross-method convergence in prefrontal function. *Neuroscience*, *139*, 327–337.

Turner, M. S., Cipolotti, L., Yousry, T. A., & Shallice, T. (2008). Confabulation: Damage to a specific inferior medial prefrontal system. *Cortex*, *44*, 637–648.

Varney, N. R. (1988). Prognostic significance of anosmia in patients with closed-head trauma. *Journal of Clinical and Experimental Neuropsychology*, *10*, 250–254.

Varrone, A., Pappata, S., Caraco, C., Soricelli, A., Milan, G., Quarantelli, M., et al. (2002). Voxel-based comparison of rCBF SPET images in frontotemporal dementia and Alzheimer's disease highlights the involvement of different cortical networks. *European Journal of Nuclear Medicine and Molecular Imaging*, *29*, 1447–1454.

Venkatraman, V., Payne, J. W., Bettman, J. R., Luce, M. F., & Huettel, S. A. (2009). Separate neural mechanisms underlie choices and strategic preferences in risky decision making. *Neuron*, *62*, 593–602.

Verberne, A. J., & Owens, N. C. (1998). Cortical modulation of the cardiovascular system. *Progress in Neurobiology*, *54*, 149–168.

Voytko, M. L. (1985). Cooling orbital frontal cortex disrupts matching-to-sample and visual discrimination learning in monkeys. *Physiological Psychology*, *13*, 219–229.

Wallis, J. D., & Kennerley, S. W. (2010). Heterogeneous reward signals in prefrontal cortex. *Current Opinion in Neurobiology*, *20*, 191–198.

Wheeler, E. Z., & Fellows, L. K. (2008). The human ventromedial frontal lobe is critical for learning from negative feedback. *Brain*, *131*, 1323–1331.

Williams, G. B., Nestor, P. J., & Hodges, J. R. (2005). Neural correlates of semantic and behavioural deficits in frontotemporal dementia. *Neuroimage*, *24*, 1042–1051.

Wilson, B., Alderman, N., Burgess, P., Emsley, H., & Evans, J. (1996). *Behavioural assessment of the dysexecutive syndrome (BADS) manual*. Bury St. Edmunds, UK: Thames Valley Test Company.

Zald, D. H., & Kim, S. W. (2001). The orbitofrontal cortex. In S. Salloway, J. D. Duffy, & P. F. Malloy (Eds.), *The frontal lobes and neuropsychiatric illness* (pp. 33–70). Washington D.C.: American Psychiatric Press.

Zald, D. H., Curtis, C., Folley, B. S., & Pardo, J. V. (2002). Prefrontal contributions to delayed spatial and object alternation: A positron emission tomography study. *Neuropsychology*, *16*, 182–189.

Zald, D. H., Curtis, C. E., Chernitsky, L. A., & Pardo, J. V. (2005). Frontal lobe activation during object alternation acquisition. *Neuropsychology*, *19*, 97–105.

Zatorre, R. J., & Jones-Gotman, M. (1991). Human olfactory discrimination after unilateral frontal or temporal lobectomy. *Brain*, *114*, 71–84.

Zgaljardic, D. J., Borod, J. C., Foldi, N. S., & Mattis, P. (2003). A review of the cognitive and behavioral sequelae of Parkinson's disease: Relationship to frontostriatal circuitry. *Cognitve and Behavioral Neurology*, *16*, 193–210.

Zorzon, M., Ukmar, M., Bragadin, L. M., Zanier, F., Antonello, R. M., Cazzato, G., et al. (2000). Olfactory dysfunction and extent of white matter abnormalities in multiple sclerosis: A clinical and MR study. *Multiple Sclerosis*, *6*, 386–390.