Frontal Lobe Contributions to Attention in Reward Learning and Decision-Making

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Abstract

Even seemingly simple decisions depend on a sophisticated ability to filter noisy inputs and select motivationally relevant options. In any given vending machine, salient soft drinks with fantastical labels and vibrant colors compete with comparatively staid bottles of water and juice. This decision environment is complex and multidimensional, with a plethora of sensory signals and action affordances rapidly presenting themselves in parallel. Navigating this landscape depends on adaptively attending to decision options and features of the environment that are motivationally relevant and predictive. Recently, there has been increased interest in how decisions are made under these demanding conditions, though the underlying neural mechanisms remain poorly understood. The frontal lobes have been separately implicated in different aspects of this problem: in allocating selective attention to behaviorally relevant information, and in learning, and making judgments, about the reward value of decision options. This doctoral work examined the interplay of attention and value-based decision processes, investigating the effects of frontal lobe damage on this interaction in patients with focal brain lesions. This investigation tested the critical contributions of frontal lobe sub-regions to directing attention to reward-predictive features in a visual search task, attributing rewards to relevant stimulus dimensions, and mediating the influence of visual fixations on decision behavior, revealing discrete functional contributions of different sub-regions to these processes. Damage to the ventromedial frontal lobe, but not other frontal sub-regions, reduced attentional selection of reward-predictive visual features, and impaired learning about features in a reward-predictive stimulus dimension. However, damage to this region did not alter the influence of visual fixations on subjects' choices. Subjects with lateral and dorsomedial frontal

damage guided attention to reward-predictive features like healthy controls, However, left lateral frontal damage increased misattribution of rewards to salient, irrelevant stimulus dimensions, while dorsomedial frontal damage increased the influence of fixations on choice behavior. These findings argue that these frontal lobe sub-regions make distinct contributions to directing selective attention during learning, and mediating the influence of attention during choice behavior. This work sheds light on the roles of the frontal lobes in facilitating adaptive choice in healthy behavior, and contributes to our understanding of how this interaction may be compromised by brain disorders.

Résumé

Les décisions les plus simples dépendent de notre capacité à filtrer l'information afin de sélectionner les options pertinentes. Toute machine distributrice, par exemple, déborde de boissons gazeuses aux étiquettes éclatantes de couleurs côtoyant des bouteilles d'eau et de jus aux allures plus sobres. Cet environnement complexe et multidimensionnel pullule de signaux sensoriels auxquels s'ajoute aussitôt un éventail d'actions possibles. Pour naviguer efficacement dans un tel environnement, une attention particulière doit être portée aux options disponibles ainsi qu'à leurs caractéristiques susceptibles de motiver nos décisions. Ces dernières années ont vu émerger un intérêt marqué envers les processus entourant la prise de décision dans ces conditions laborieuses, ainsi qu'envers la description des mécanismes neuronaux sous-jacents, encore méconnus. Notamment, les lobes frontaux ont été impliqués dans différentes facettes de ce problème, étudiées séparément : dans l'allocation de l'attention sélective vers l'information importante à la réalisation d'une tâche, ainsi que dans l'apprentissage de la valeur associée aux stimuli et dans les jugements de la valeur des options de choix fondés sur la récompense. Cette thèse doctorale décrit la relation entre l'attention et la prise de décision fondée sur la valeur en observant les effets résultants de dommages aux lobes frontaux sur cette interaction chez des patients présentant de lésions cérébrales focales. Ces travaux de recherche ont étudié l'effet de lésions frontales sur l'orientation de l'attention vers les attributs qui sont prédicteurs de récompenses lors d'une tâche de recherche visuelle, dans l'attribution de la récompense aux dimensions des stimuli qui la prédisent et sur l'influence des fixations oculaires dans la prise de décision. Ces travaux ont révélé des rôles distincts des sous-régions des lobes frontaux lors de ces tâches expérimentales. Les lésions touchant le lobe

frontal ventromédian, épargnant les autres sous-régions frontales, atténuent l'orientation de l'attention vers les attributs prédicteurs de récompense, en plus d'affecter la capacité d'apprendre quelle dimension des stimuli prédit effectivement la récompense. Par contre, une lésion à cette région n'altère pas l'influence qu'ont les fixations oculaires sur les choix des patients. Bien que les dommages aux régions frontales latérale et dorsomédiale laissent intacte l'allocation de l'attention aux attributs récompensés, les patient lésés au lobe frontal latéral gauche associent davantage la récompense à une dimension des stimuli qui ne la prédit aucunement, alors qu'en cas de lésion de la région dorsomédiale, les fixations oculaires exercent une influence exagérée sur les choix des patients. Ces résultats suggèrent que les sous-régions des lobes frontaux ont des rôles distincts dans l'orientation de l'attention sélective lors de l'apprentissage ainsi que dans la mise en place des processus attentionnels au moment de prendre des décisions et de faire des choix. En plus d'apporter des précisions quant aux contributions des lobes frontaux à la mise en œuvre de choix adéquats favorisant un comportement sain, ces travaux aident à comprendre comment ces interactions peuvent-être compromises en cas de troubles neurologiques ou psychiatriques.

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The ensuing pages will argue about the importance of considered, deliberate decisions in demanding situations. However, it was mostly good fortune that I happened (drifted? diffused?) into the lab or my supervisor, Dr. Lesley Fellows. Her invaluable mentorship has been critical at every step in this PhD program. It has been her generosity, commitment to high standards, and appreciation for puns that have lighted the way through this work. I am deeply grateful to have been her student.

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Contributions of the authors

In accordance with the guidelines of McGill University Graduate and Postdoctoral Studies for manuscript-based theses, the contributions of the authors are described here.

This thesis integrates three manuscripts presenting original research:

Study 1 (Chapter 2)

Vaidya A.R., and Fellows L. K. (2015). Ventromedial frontal damage in humans reduces attentional priming of rewarded visual features. *The Journal of Neuroscience*, 35(37).

Study 2 (Chapter 3)

Vaidya A.R., and Fellows L.K. Necessary contributions of human frontal lobe sub-regions to reward learning in a dynamic, multidimensional environment. *In preparation.*

Study 3 (Chapter 4)

Vaidya A.R., and Fellows L. K. 2015. Testing necessary regional frontal contributions to value assessment and fixation-based updating. *Nature Communications,* 6 :10120*.*

In each of these studies, Avinash R. Vaidya planned the experiment, collected and analyzed the data and drafted the manuscript. Lesley K. Fellows was involved in the conceptualization of each study, and provided constructive input on the analysis of the data, as well as critical revisions and final approval on each manuscript.

Other contributions

Vaidya A.R., and Fellows L.K. The Neuropsychology of Decision-Making: A View from the Frontal Lobes. Eds. Dreher J-C. & Tremblay L. Decision Neuroscience: Handbook of Reward and Decision-Making. Elsevier, United Kingdom*. In press.*

Vaidya A.R. Neural mechanisms for undoing the "curse of dimensionality." (2015). *The Journal of Neuroscience*, 35(35).

Vaidya A.R., Jin, C., and Fellows L. K. (2014). Eye spy: The predictive value of fixation patterns in detecting subtle and extreme emotions from faces. *Cognition,* 133(2).

Hochman E.Y., Vaidya A.R., and Fellows L.K. (2014). Evidence of a role for the dorsal anterior cingulate cortex in disengaging from an incorrect response. *PLoS One,* 9(6).

Chapter 1: Introduction

The Russian neuropsychologist Luria (1966) described a "basic paradox" confronting studies of frontal lobe lesions, noting that "Individual specialized functions (sensation and movement, vision and hearing, speech and formal intellectual operations) may be adequately preserved in such patients but behavior as a whole is overtly pathological." This dichotomy is echoed in many early studies of frontal lobe damage in humans and animal models: while some found that formal intellectual functions were mostly intact after dramatic frontal lesions (Hebb & Penfield, 1940; Teuber, Battersby, & Bender, 1951), others described radical alterations in conduct and purposeful, motivated behavior (Bianchi, 1895; Harlow 1868). The cryptic quality of these deficits seemed to largely defy early attempts at physiological or psychological explanation, making the frontal lobes a kind of cerebral "*terra incognita*" (Penfield & Evans, 1935).

Subsequent work has pushed the frontier of our knowledge of frontal lobe function. Predominantly, these investigations have focused on the role of this region in organizing behavior and achieving instructed goals. Many studies have now shown that the frontal lobes are critical for directing attention to features of the environment that are relevant for the task at hand. Accounts originating from this work argue that the frontal lobes are critical for exerting cognitive control and selective attention to adaptively regulate internal mental processes, especially when faced with distractions and sensory noise.

Critically, these studies have not adequately addressed the mechanisms underlying other deficits classically associated with frontal damage, particularly impairments in social and motivated behavior. Investigators have begun to broach this problem, uncovering a

circuit of brain areas involved in reward-based learning and decision-making, including frontal lobe sub-regions. Until recently, this effort has largely minimized or ignored the role of attention in these decision processes. However, it is increasingly clear that any comprehensive account of the neurobiology of decision-making must address the interaction of attention and motivation. While the frontal lobes are frequently invoked separately as key in these processes, their potential role in the interplay between these processes has not been addressed. Moreover, studies of the neurobiology of decision-making in humans have relied mostly on correlative measures of brain activity, and are not informed by lesion evidence. Hence the necessary contributions of the frontal lobes to motivated choice behavior are not well understood.

This thesis examines the contributions of the frontal lobes to guiding attention during learning and decision-making through loss-of-function testing of patients with focal lesion damage. In this chapter, I will first describe the anatomical sub-divisions of the frontal lobes, followed by a review of the functional roles attributed to the frontal lobes in attention and decision-making. I will then describe known interactions between attention and decision-making, leading to the specific aims of this thesis. The following three chapters present studies focusing on the role of frontal sub-regions in attentional processes during reward-based learning and choice tasks. First, testing the effects of frontal damage on guiding attention to reward-predictive stimulus features (chapter 2), then on selecting between relevant and irrelevant stimulus dimensions during a reward learning task (chapter 3) and finally, on the influence of attention during choice (chapter 4). In the final chapter, I will discuss the overall conclusions from this work and describe how these

studies together inform our understanding of the contributions of the frontal lobes to attention and motivated behavior.

Anatomical subdivisions of the frontal lobes

This section briefly reviews the anatomical divisions of the frontal lobes, with an emphasis on how these regions are separated in this thesis. The anatomical boundaries of frontal lobe sub-regions described in this work respect the patterns of lesion damage found in focal lesion samples, and are commonly used in neuropsychological studies (Stuss & Levine, 2002; Stuss, Shallice, Alexander, & Picton, 1995). In brief, these sub-regions include the dorsomedial frontal lobes (DMF) comprised of the dorsal medial wall and anterior cingulate cortex (ACC), the lateral frontal lobes (LF) including dorsolateral and ventrolateral prefrontal cortex, and the ventromedial frontal cortex (VMF) including the orbitofrontal cortex (OFC), frontal polar cortex and the ventral ACC.

Figure 1.1 shows the borders used to define these broad regions of interest, superimposed on an overlap image of the lesion tracings of 54 patients with frontal lobe damage tested in this thesis work, classified according to the above subdivisions. This figure demonstrates the extent of lesion coverage in the experiments described here, and how well focal lesions affecting these sub-regions can be segregated according to these *a priori* borders. It also shows some of the limitations of the region-of-interest (ROI) method: damage can extend across regional boundaries, and some regions may be better represented than others. These issues can be mitigated somewhat by the use of voxel-wise comparisons of behavior to test where damage is related to deficits without any *a priori* grouping (Bates et al., 2003). The following sections will briefly review the anatomy and connective profiles of these frontal lobe sub-regions.

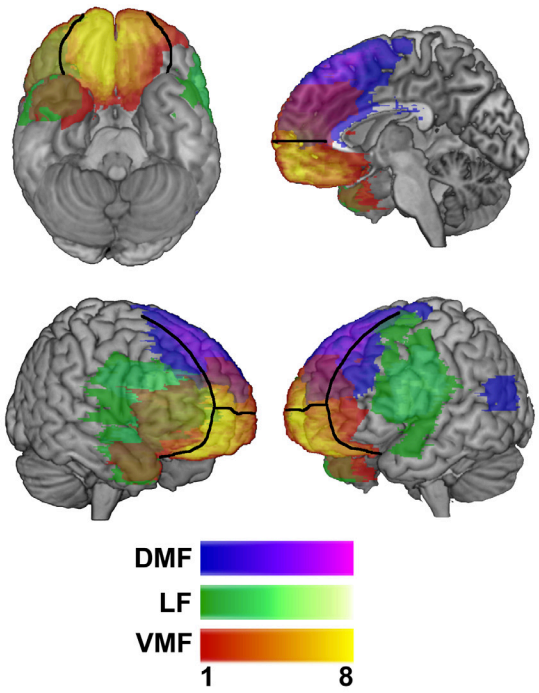

Figure 1.1. Overlap map showing lesion tracings for all patients included in this thesis work overlaid on the MNI brain in three-dimensional views. Maps are colored by group category. Black lines represent boundaries for the assignment of patients to particular lesion groups. Color scale indicates the number of patients.

Dorsomedial frontal lobe

DMF is comprised of the ACC and medial superior frontal gyrus dorsal to the genu of the corpus callosum. These regions can be subdivided into cytoarchitectonic areas described by Brodmann (1909) and subsequently updated and revised by (Petrides & Pandya, 1994) based on comparative study of human and monkey cortical areas. The superior frontal gyrus includes PPA (Petrides and Pandya area) 8, 9 and the anterior 6. PPA 6 includes the supplementary motor area (SMA) and pre-SMA, as well as the supplementary eye fields (SEFs). Retrograde tracer studies in monkeys have found that the SMA is directly connected with corticospinal neurons and primary motor cortex. These projections are more sparse in the pre-SMA, which is better connected with dorsolateral prefrontal cortex (see Nachev, Kennard, & Husain, 2008 for a review). Both SMA and pre-

SMA receive major input from the internal segment of the globus pallidus via the thalamus, and have direct connections to the subthalamic nucleus via a 'hyperdirect' cortical-basal ganglia pathway (Nambu, Tokuno, & Takada, 2002), which may provide a cortical mechanism for directly stopping ongoing actions (Wiecki & Frank, 2013).

The dorsal ACC is subdivided into PPA 24' and 32', with the latter comprised of several somatotopically organized motor areas (Amiez & Petrides, 2014; Picard & Strick, 1996). The dorsal ACC in monkeys is intimately connected with the SMA and primary motor cortex and, like the SMA, has direct connections with corticospinal motor neurons (reviewed in Paus, 2001). The dorsolateral prefrontal cortex is a major projection site for the ACC, and the two areas are thought to work together in settings that demand cognitive control (MacDonald, Cohen, Stenger, & Carter, 2000). Both the ACC and SMA are major targets for dopaminergic neurons in the midbrain, which may have an important facilitating role for action selection and learning processes that depend on these regions (Rushworth, Noonan, Boorman, Walton, & Behrens, 2011).

Lateral frontal lobe

LF includes both the dorsolateral (DLPFC) and ventrolateral prefrontal cortex (VLPFC). DLPFC includes the lateral part of the superior frontal gyrus and middle frontal gyrus, comprised of PPA 8, 9, 46 and 9/46. VLPFC consists of the inferior frontal gyrus, including of PPA 44, 45 and 47/12. These regions have distinct patterns of connectivity and function. Studies in monkeys have found that the DLPFC is connected with the multimodal superior temporal sulcus, as well as paralimbic regions including the anterior and posterior cingulate and retrosplenial cortex (Petrides & Pandya, 1999). Caudally, the DLPFC is bidirectionally connected with the superior and inferior parietal lobules, which are

important for visuo-spatial processing and hand and eye movements (reviewed by Petrides, 2005). Caudal DLPFC also includes the frontal eye fields, a region with bidirectional connections to relatively early visual areas in temporal and parietal cortex, and which has a critical role in eye-movements and attention (Barbas, 2000; Corbetta & Shulman, 2002).

Like DLPFC, the VLPFC also has robust connections with the multimodal superior temporal sulcus through PPA 45, as well as connections with visual association cortex within inferotemporal cortex and perirhinal and parahippocampal cortex via PPA 47/12 (Petrides & Pandya, 2002). In both humans and macaque monkeys, PPA 44 and 45, which together comprise Broca's area, make additional connections with the inferior parietal lobule, and auditory association cortex in the superior and middle temporal gyri, connections thought to be functionally important in language and speech in the left hemisphere (Petrides, Tomaiuolo, Yeterian, & Pandya, 2012).

Functionally, the lateral prefrontal cortex has been suggested to have a rostral-caudal gradient of complexity, with more caudal regions involved in simpler motor transformations, and anterior regions involved in working memory and selective attention processes based on increasingly abstract criteria in more rostral areas (Badre, Hoffman, Cooney, & D'Esposito, 2009; Petrides, 2005). This hypothesis derives in part from the connectivity patterns of these regions, with more anterior regions connected to other 'higher-order' areas in the parietal and temporal lobes, and posterior regions more directly connected with sensorimotor cortex. Lateral PFC also projects to the rostral striatum, innervating the head of the caudate nucleus and putamen. Lateral PFC and the caudate nucleus are both functionally involved in working memory tasks, a role potentially

mediated, or supported, by the connections between these two regions (reviewed in Haber, 2003).

Ventromedial frontal lobe

VMF refers to central orbitofrontal cortex (OFC), including PPA 11, 13, 14, as well as frontal polar cortex (PPA 10) and ventral ACC, inferior to the genu of the corpus callosum (PPA 24, 32, 25). Human functional imaging studies often report activations in a region termed ventromedial prefrontal cortex (vmPFC), referring to an area spanning the ventral medial wall, including the medial OFC, ventral ACC and frontal pole (Bartra, McGuire, & Kable, 2013; Pearson, Watson, & Platt, 2014). VMF, as defined here, includes this area as well as the central OFC, bordered laterally by PPA 47/12 in VLPFC.

Sub-regions within monkey OFC form two internal networks — an 'orbital' network of areas in central OFC (PPA 11 and 13) and a 'medial' network (PPA 11m and 14), which are in turn also well connected with each other and PPA 47/12 (Price, 2007). Retrograde tracer studies in monkeys indicate that posterior OFC is exceptional among frontal regions for the convergent bidirectional connections it shares with multiple sensory systems, including visual, auditory, somatosensory and olfactory regions (Barbas, 2000). Highly focal deactivation studies have implicated this region in sensory specific value updating, suggesting a key role in mediating links between sensory signals and endogenous representations of reward value (Murray, Moylan, Saleem, Basile, & Turchi, 2015). The amygdala, posterior OFC (caudal PPA 13 and orbital peri-allocortex and pro-isocortex) and mediodorsal nucleus of the thalamus form a contained circuit that may be critical in mediating the processing of emotions. Posterior OFC has also been suggested as a mediator of sensory information through projections to the thalamic reticular nucleus (reviewed in

Barbas, Zikopoulos, & Timbie, 2011). In contrast, medial OFC has few sensory connections, but sends projections to the ventral striatum (Haber, 2003), and is well connected with the hypothalamus and midbrain (Barbas, 2000). The amygdala, hippocampus, entorhinal and parahippocampal cortex are also connected with both internal OFC networks, albeit more robustly with medial regions (Price, 2007). It has been suggested that these convergent connections give OFC special access to signals necessary for connecting stimuli with predicted rewards (Rolls, 2006).

The ventral ACC has connections similar to the medial OFC, including projections to the ventral striatum overlapping with OFC terminals (Haber, 2003). However, sensory inputs and connections to the amygdala are sparser in this region than in the OFC, while connections with the hippocampus are more dense (Barbas, 2000). Frontal polar cortex has reciprocal connections predominantly with regions of prefrontal cortex (PFC) and anterior temporal cortex, but has notably few connections with sensory areas (reviewed in Ramnani & Owen, 2004). This connectivity profile has helped prompt the suggestion that the frontal poles are important in 'meta-cognitive' processes, potentially monitoring goal-related activity in other PFC regions (Petrides, 2005). Both the frontal pole and ventral ACC are also thought to be involved in affect, and may become dysfunctional in mood disorders (Drevets, 2001; Stuss & Levine, 2002).

Attention and the frontal lobes

Attentional accounts of frontal lobe function can be traced back to at least Ferrier (1876). He described the aimless behavior of animals with radical frontal excisions as arising from a failure to appropriately direct attention for the facilitation of processing

external stimuli, and internal mental processes. However, attention can be a slippery construct to define, and takes many forms in different literatures. James (1890) wrote

> Every one knows what attention is. It is the taking possession by the mind, clear and vivid form, one out what seem several simultaneously possible objects trains of thought. Focalization, concentration, of consciousness are of its essence. It implies withdrawal from some things in order to deal effectively with others. (pp. 403-404)

Contemporary definitions of attention have been built on this intuitive view: in more contemporary terms, stressing the preferential allocation of processing resources to some information to the exclusion of other information. Several different forms of attention have been identified, distinguished by the type of information undergoing processing (e.g. spatial attention, feature attention), and possibly by their underlying neural mechanisms. While much work has investigated the neural basis of attention in goal-directed behavior, there has been an increased awareness that attention may be engaged in other contexts and for different purposes (e.g. attention for action versus attention for learning or attention for liking) (Gottlieb, 2012; Hogarth, Dickinson, & Duka, 2010). In this thesis, I will describe the effects of frontal lobe damage on some of these different attentional processes. Thus, I will briefly review the measurement and operationalization of attention in some of the different forms that will be examined in this work. I will then briefly describe frontal lobe contributions to the direction and control of attention for adaptive behavior. As the experiments in this thesis focus on processing of visual stimuli, this review will emphasize visual attention, although many of the concepts discussed may not be unique to vision.

Measurement of attention

The definition of attention given by James (1890) describes the essential qualities underlying experimental measurement. Within most studies, attention is measured through the improved processing of some content currently in the attentional 'spotlight,' and worsened processing of other, un-attended content. This content may be some external stimulus, but could also be an internal representation, or action. The deployment of attention might be overt (i.e. orienting of head or eyes), or covert (i.e. an internal shift in attention without any outward movement toward a stimulus). Overt eye-movements shift the foveae to stimuli for optimal processing of fine detail, while simultaneously placing surrounding stimuli in the periphery of the retina, where acuity is lower. The assumption, which underlies many studies using eye-movements as a tool to study attention, is that fixations are directed to stimuli that are currently being attended for the purpose of gathering visual information. Thus, by recording the movements of the eye, one might be able to infer where attention is being directed. While this assumption may be true in most ecological settings (Hoffman & Subramaniam, 1995), visual attention and eye movements can be uncoupled experimentally, and this assumption may not always be met (Remington, 1980).

Internal shifts of attention can be inferred behaviorally. Attended stimuli are detected or discriminated faster and more accurately than un-attended stimuli. Studies examining attention of this kind often use statistical regularities in the task design to shift attention: in a classic example, Posner (1980) showed that predictive spatial cues improved detection of targets appearing in the cued location compared to targets preceded by an invalid cue, or no cue, while the eyes were stationary. The features of a stimulus (e.g.

color, motion, shape) can also capture attention when predictive of target identity (Kristjansson & Campana, 2010; Maljkovic & Nakayama, 1994). In contrast, ecological, emotionally charged or rewarding stimuli (e.g. faces or violent images) automatically grab attention without any experimental training (McHugo, Olatunji, & Zald, 2013; Vuilleumier & Driver, 2007). Similarly, stimuli with greater perceptual salience (e.g. large, high contrast, high luminance) are also targets for automatic covert and overt attention (Corbetta & Shulman, 2002; Walther & Koch, 2006). Thus, perceptual processing is affected by the internal allocation of attention based on learned predictive value and perceptual or affective salience.

A separate, but very much related, literature has investigated the influence of attention in learning. Again, James (1890) provided an early intuitive description of this interaction, writing that "an object once attended to will remain in the memory, whilst one inattentively passed will leave no traces behind." Attentional theories of associative learning reflect this idea, describing attention as a process modulating the degree to which outcomes are attributed to cues (Kruschke, 2001; Mackintosh, 1975; Pearce & Hall, 1980). Attention, in this context, is inferred through subsequent behavior following a learning experience. Here, attentional effects on learning are measured by the relative influence of different cue-feedback associations on future behavior (Kruschke, 2003) .

Frontal contributions to goal-directed attention

The ability to internally control selective attention is critical for achieving endogenous goals. Hebb (1949) emphasized the relevance of attentional phenomena of this kind as a critical foundation for rejecting the notion that behavior can be explained simply as a series of reactions to external stimuli. Many prominent theories of attention (e.g.

Corbetta and Shulman (2002); Desimone and Duncan (1995); Norman and Shallice (1983)) conceive of attentional selection as a competitive process with neural representations of potential targets vying for the attentional spotlight, or otherwise limited processing resources. These accounts refer generally to two different systems that may influence attention: 'bottom-up' or 'stimulus-driven' systems that allow attention to be captured based on the salient features of the stimulus itself (e.g. a bright flash, a loud bang), and 'top-down' or 'goal-directed' systems that involve willful control of attention, usually for goal directed behavior. These accounts focus on the frontal lobes as a potential source for these goal-based influences. Attentional signals originating in prefrontal cortex (PFC) are thought to modulate activity in perceptual, sensory and motor regions, biasing processing in these areas for some purposeful end. In this framework, such signals are thought to be especially important for overcoming competition from salient, but irrelevant, cues that may act as distractors, competing with goal-relevant stimuli (Miller & Cohen, 2001).

These views of frontal lobe function have broad support from different experimental approaches. Several studies have found that patients with frontal lobe damage, particularly to the lateral frontal lobes, are more sensitive to the distracting influence of irrelevant, interfering stimuli in tests of selective attention (Glascher et al., 2012; Perret, 1974; Tsuchida & Fellows, 2013) and memory (Chao & Knight, 1998; Shimamura, Jurica, Mangels, Gershberg, & Knight, 1995; Tsuchida & Fellows, 2009). Electrophysiological recordings in macaque lateral PFC also support the notion that this region actively facilitates goal-directed attentional selection. Target selective activity in PFC precedes similar signals in posterior visual areas when these targets are non-salient (Buschman & Miller, 2007), and is more resistant to the introduction of salient distractors

compared to other regions, with the degree of resistance predicting task performance (Suzuki & Gottlieb, 2013; Tremblay, Pieper, Sachs, & Martinez-Trujillo, 2015). Damage to this region has also been shown to affect the ability to shift attention between stimulus dimensions in variants of the Wisconsin Card Sort Task (i.e. extra-dimensional shifting) in humans and monkeys (Dias, Robbins, & Roberts, 1996b; Milner, 1963), though other work has also implicated the DMF in this task (Glascher et al., 2012).

The extent to which PFC function can be described as unitary, and the degree of functional specialization in different PFC sub-regions, has been heavily debated. The deficits of PFC damaged patients in selective attention, and cognitive control more generally, have been described as resulting from a kind of general 'goal neglect,' an inability to maintain task goals over an extended period of time, despite explicitly comprehending their meaning (Duncan, Emslie, Williams, Johnson, & Freer, 1996). This account argues that different 'executive functions' attributed to the frontal lobes, such as selective attention or working memory, can be accounted for by a role in activating representation of goals, related strongly to performance in a wide range of cognitive tasks and captured by fluid intelligence, or *g* (Duncan, Burgess, & Emslie, 1995; Duncan, Johnson, Swales, & Freer, 1997). In a similar vein, Miller and Cohen (2001) argued that PFC has a general role in providing a 'top-down' control signal that applies task instructions by biasing competition in other regions. This perspective suggests a general role for PFC in biasing processing not just in classic visual attention tasks, but also in the activation of memories, or selection of actions.

Notably, lesion studies involving large samples of patients with focal frontal lobe damage have been able to test the degree of functional specificity in human frontal lobe

sub-regions. This work has demonstrated the existence of consistent, dissociable behavioral deficits in tasks tapping different cognitive functions (reviewed by Stuss & Levine, 2002). For example, LF and DMF, but not VMF, have been shown to be principally involved in tasks requiring selective attention or working memory in the face of interference, particularly of the kind focused on by domain-general accounts of PFC function (Glascher et al., 2012; Thompson-Schill et al., 2002; Tsuchida & Fellows, 2013). Impairments may also be lateralized and content-dependent (i.e. involving verbal versus non-verbal material), particularly in the case of LF damaged patients (Geddes, Tsuchida, Ashley, Swick, & Fellows, 2014).

An alternative view suggests that the functions of frontal sub-regions are not truly discrete, but separate manifestations of a general control process acting in different modalities, or on different types of content (Thompson-Schill, Bedny, & Goldberg, 2005). More recent computational theories suggest that PFC sub-regions, particularly lateral and dorsomedial PFC, may be hierarchically organized, with similar underlying function, but processing increasingly abstract content (Alexander & Brown, 2015; Frank & Badre, 2012). Altogether, lesion work supports the specialization of frontal sub-regions, and more recent theoretical accounts acknowledge some regional specialization within the frontal lobes.

Frontal contributions to neglect

Frontal lobe damage, predominantly to the right hemisphere, can also affect attention to contralesional space, particularly in the acute phase of damage. Frontal lesions may result in both perceptual and motor neglect contralesionally, respectively marked by a failure to attend to stimuli presented in contralesional space, and a paucity of spontaneous action from contralesional effectors, despite otherwise intact sensory and motor functions

(Husain, 2002; Mesulam, 1999). Functional imaging suggests that lesions to the right perisylvian cortex affect the symmetry of attentional responses to contralesional space, particularly in the acute phase of brain damage (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005). This dysfunctional imbalance in interhemispheric competition between activity in perceptual and motor areas has been suggested to underlie the symptoms of neglect, as representations of stimuli and actions in the lesioned hemisphere can no longer compete with their counterparts on the opposite side (Corbetta & Shulman, 2011).

Frontal lobes and decision-making

As summarized above, a large number of studies have established the general importance of the frontal lobes in attention and guiding behavior for achieving experimentally imposed goals. However, in reality, behavior is often a product of motivational forces shaped by a complex interaction of internal drives and extrinsic incentives (Bindra, 1969). Behavioral economists and psychologists have had a longstanding interest in how individuals make decisions based on motivationally relevant outcomes (e.g. the promise of a sip of juice, or a check in the mail). Only recently have neurobiologists ventured into this territory, with the aim of developing a physiological model of how such choices are made. This work has uncovered a circuit of cortical and subcortical structures that appear to have a special role in making choices based on, and learning about, the motivational properties of stimulus options (Haber & Knutson, 2010). This section briefly reviews different neurobiological accounts of these processes, with an emphasis on investigations of frontal lobe contributions.

Frontal contributions to value-based choice

Within economic accounts of decision-making, normative choice behavior depends on the comparison of options based on 'subjective value' (i.e. the integrated rewards and costs, as perceived by the agent making a choice). For a rational decision agent, choices should always maximize subjective value and be internally consistent (von Neumann & Morgenstern, 1944). Several decades of research have consistently found that humans do not act in this rational way, but instead demonstrate a number of irrational biases (e.g. loss aversion (Kahneman, 2003)). However, this conception of decisions guided by a common value construct is a central theme within computational, psychological and economic perspectives of decision-making and learning (Kable & Glimcher, 2009). As a result, this construct has been an influential starting point for many different approaches investigating the underpinnings of decision behavior.

Many studies have now shown that brain activity in a common network of regions correlates with subjective value for many different types of reward (e.g. food, money, trinkets) (Chib, Rangel, Shimojo, & O'Doherty, 2009; Levy & Glimcher, 2012). Simply presenting subjects with these options and asking them to rate the options on a scale, or bid on how much they would want to have them, can provide information about the subjective value subjects assign to these items (Rangel & Clithero, 2013). Single-cell recordings in monkeys (Padoa-Schioppa & Assad, 2006; Thorpe, Rolls, & Maddison, 1983), and an abundance of functional imaging studies in humans (see meta-analyses in Bartra et al., 2013; Clithero & Rangel, 2014), have found evidence that subjective value correlates with activity in OFC and vmPFC. However, studies of different species usually target different areas, with non-human primate work mostly recording value signals in central

OFC, and human imaging studies finding value correlates in vmPFC (Wallis, 2011). Imaging work has also pointed to a role for vmPFC in integrating value signals for different attributes (Lim, O'Doherty, & Rangel, 2013; Philiastides, Biele, & Heekeren, 2010), and across stimulus categories (McNamee, Rangel, & O'Doherty, 2013), arguing that this region has a central role in forming a common subjective value code from multiple sources of information.

Lesions to human VMF have been found to impair value-based decision-making. Namely, patients with damage to this region make internally inconsistent value-based choices, a pattern present across many different types of stimuli (e.g. vegetables, landscapes, puppies), but are as internally consistent as control subjects for similar perceptual choices (Camille, Griffiths, Vo, Fellows, & Kable, 2011; Fellows & Farah, 2007; Henri-Bhargava, Simioni, & Fellows, 2012). Internal inconsistency of preferences (i.e. transitivity errors) violate a central property of rational choice (von Neumann & Morgenstern, 1944), suggesting a fundamental deficit in value assessment or comparison. Similar results have also been reported in OFC lesioned monkeys (Baylis & Gaffan, 1991), lending support to this hypothesis.

Within the frontal lobes, hemodynamic subjective value signals have also been observed in the anterior insula, supplementary motor area (SMA) and ACC across several studies (Bartra et al., 2013). However, the extent to which these signals can be differentiated from general motivational signals (i.e. salience) is unclear (Litt, Plassmann, Shiv, & Rangel, 2011). In particular, the functional significance of value signals within the ACC and SMA, have been heavily debated. Some work argues that these regions may have a specific role in assessing information relevant to value-based decisions in the action

domain (e.g. effort) (Walton, Bannerman, Alterescu, & Rushworth, 2003). Recent imaging and electrophysiological studies have proposed that the dorsal ACC represents the value of alternative courses of action during foraging tasks (Kolling, Behrens, Mars, & Rushworth, 2012; Quilodran, Rothe, & Procyk, 2008). Other work has contested this view (Shenhav, Straccia, Cohen, & Botvinick, 2014), instead arguing that this region detects 'conflict' between decision options (Botvinick, Braver, Barch, Carter, & Cohen, 2001). While there is general agreement that this region is involved in utilizing value information during action selection (Shenhav, Botvinick, & Cohen, 2013), the exact functional role that this region plays in these settings remains up for debate.

Frontal contributions to value-based learning

A related literature has examined the role of the frontal lobes in learning about reward value associations in the environment. Unlike the work reviewed above, learning tasks generally manipulate the value associations of otherwise neutral stimuli. Rather than forming a subjective value assessment for an option, these tasks demand tracking the value history of an option over an extended period.

The importance of the frontal lobes in learning value associations has been established repeatedly through studies of lesions in human patients and monkeys. In particular, the frontal lobes appear to be critical when these value associations are dynamic. Several early studies showed that damage to OFC in monkeys (Butter, 1968; Dias, Robbins, & Roberts, 1996a; B. Jones & Mishkin, 1972), and VMF in humans (Fellows & Farah, 2003; Hornak et al., 2004), impair learning when deterministically set stimulus-reward associations are reversed, while leaving initial deterministic learning (i.e. conditional discrimination) intact. Similar deficits were observed in human patients in the

Iowa Gambling Task (IGT), where subjects chose from four decks of cards, each with a preset schedule of rewards and punishments (Bechara, Damasio, Damasio, & Anderson, 1994; Glascher et al., 2012). Impairments in the IGT have been shown to depend on the ordering of cards in these decks, and are likely closely related to reversal learning deficits (Fellows & Farah, 2005a).

Deficits in reversal learning following OFC damage have been interpreted as a failure to inhibit response tendencies (Butter, 1968; B. Jones & Mishkin, 1972), or a deficit in switching attentional selection based on changing affective associations (Dias et al., 1996a). More recent interpretations instead emphasize the importance of this region in forming stimulus-reward associations, arguing that learning deficits are not necessarily specific to reversal. OFC damage in monkeys can impair learning when reward contingencies are probabilistic, even in the absence of reversals (Noonan et al., 2010; Rudebeck, Behrens, et al., 2008). Similarly, patients with VMF damage made more errors in a probabilistic reversal learning task compared to other subjects, even before a reversal occurred (Tsuchida, Doll, & Fellows, 2010). While generally thought to reflect reward learning, the mechanism underlying these deficits still remains unclear. Recent work has argued that OFC damage disrupts the integrity of learned links between specific choices and rewards in recent trials. Walton, Behrens, Buckley, Rudebeck, and Rushworth (2010) showed that monkeys with OFC damage misattributed feedback to temporally proximate choices, a manifestation of a learning phenomenon known as 'spread-of-effect' (Thorndike, 1933). This finding was taken to suggest a role for this region in 'credit assignment' — i.e. the appropriate attribution of outcomes to antecedent choices or cues.

The common involvement of VMF in both learning and making choices based on subjective value has been taken as evidence for the critical role of this region in processing value information more generally. However, other work has called this view into question. The presence of signals reflecting subjective value and value comparison outside of OFC and vmPFC argues against a unique role for these regions in computing this information (Kennerley, Behrens, & Wallis, 2011; Strait, Sleezer, & Hayden, 2015). A recent study showed that asking monkeys to perform a task with intermingled effort and delay-based choices resulted in a loss of subjective value coding in OFC. Instead, OFC neurons encoded the decision type for the trial at hand, indicating that subjective value coding may just be one potential variable coded in OFC (Hosokawa, Kennerley, Sloan, & Wallis, 2013). Other studies have found that OFC lesioned monkeys can update the values of foods following selective satiety, though not cues paired with these food rewards (Izquierdo, Suda, & Murray, 2004). A recent study has even raised questions about the necessity of OFC in classic reversal learning tasks, arguing that deficits in OFC lesioned monkeys may be the consequence of interruptions in the underlying white matter (Rudebeck, Saunders, Prescott, Chau, & Murray, 2013). Recent work in rats has similarly found that inactivation or lesioning of OFC impairs the ability to make choices based on values that have to be inferred through association, but not values learned through direct conditioning (Bradfield, Dezfouli, van Holstein, Chieng, & Balleine, 2015; J. L. Jones et al., 2012b). While supporting some functional contribution for this region in value-based choice, these recent studies indicate that role may be more nuanced.

Notably, OFC/VMF is also not critical for all forms of value-based learning. Learning about which movements are more rewarding or costly ('action-value'), depends on DMF,

and not VMF. Rudebeck, Behrens, et al. (2008) demonstrated that monkeys with OFC damage could learn to choose between two actions with deterministic and probabilistic reward contingencies just as well as controls, even when these same animals were impaired in learning stimulus-value associations in a task with identical probabilities. In contrast, animals with ACC lesions showed the opposite pattern of behavior. A similar double dissociation has also been demonstrated in human patients (Camille, Tsuchida, & Fellows, 2011). These findings indicate the presence of distinct systems for learning about and assessing actions and stimuli based on their value (Rushworth et al., 2011), arguing against the existence of a unitary system for value learning and comparison.

Interactions between attention and decision-making

Many neurobiological accounts of economic decision-making lean heavily on the construct of subjective value as an explanatory variable underlying choice behavior. A critical assumption of this framework is that the rewards and costs associated with complex multi-faceted options in real-life decisions are weighted and integrated into these value assessments (Rangel & Clithero, 2013). However, the mechanisms in play for weighting and selecting these features, or attributes, are complex and change from person to person and between task settings (Payne, Bettman, & Johnson, 1993). Moreover, not all features necessarily have the same predictive value, and hence it may sometimes be critical to adaptively focus on features that are particularly informative (i.e. predictive of future outcomes). Recent work has looked to attentional explanations for understanding how option features are selected to support adaptive decision-making. This section will briefly review work examining the effects of value associations on attention, and the role of attention in value-based learning and decision-making.

Value effects on attention

As reviewed earlier, many accounts argue that the frontal lobes have a critical role in top-down guidance of attention for goal-directed behavior. While task goals and rewards are aligned in most studies, selection based on current goals or reward expectancy may be mechanistically distinct (Maunsell, 2004). Recent work has indeed shown that goals and rewards can independently compete with each other for attentional priority when experimentally orthogonalized. Stimulus features associated with rewarding feedback can facilitate or impede performance during visual search when present as distractors or targets, respectively (Anderson, Laurent, & Yantis, 2011b; Della Libera & Chelazzi, 2009a; Hickey, Chelazzi, & Theeuwes, 2010a). These attentional biases depend on the integrated history of recent feedback, and may be relatively dynamic (Kristjansson, Sigurjonsdottir, & Driver, 2010), but can also become ingrained and long lasting with more extensive training (Anderson et al., 2011b; Della Libera & Chelazzi, 2009a). A growing literature has emphasized the ubiquity of motivational effects on performance across multiple modalities, showing both complimentary and conflicting interactions between goals and value on perception and action selection (Liston & Stone, 2008; Milstein & Dorris, 2007; Small et al., 2005). This work has led to the suggestion that reward-derived signals are a feature of perception and cognition, not just a 'bug' or confound of task design (Pessoa, 2015).

Reward associations affect sensorimotor activity, such that neural populations encoding responding to visual targets or potential movements are more active when paired with higher reward value (Hickey et al., 2010a; Kiss, Driver, & Eimer, 2009; Pastor-Bernier & Cisek, 2011; Serences, 2008). However, the degree to which these signals can be genuinely described as reflecting 'value,' as opposed to signals more generally related to

salience or arousal, has been subject to debate. Some work has shown that putative value signals in premotor and higher order sensory regions may be better described as responses to motivational relevance (i.e. expectation of either punishment or reward rather than 'value' per se) (Litt et al., 2011; Roesch & Olson, 2004). This view argues that reward value expectations are represented within a more restricted set of cortical and subcortical structures (e.g. vmPFC, ventral striatum) that influence downstream sensorimotor regions, resulting in motivationally-dependent modulation of activity (Roesch & Olson, 2007). However, other accounts argue that these signals are a manifestation of the biased competition between the sensorimotor representations of decision options. In this context, these effects of reward-value or motivational salience on sensorimotor activity are interpreted as the mechanism underlying motivated decision-making, and are therefore of critical relevance (Cisek, 2012).

Relatively little is known about the neurophysiological origins of these reward biases. Functional imaging work has argued that a network of frontal, parietal and subcortical regions underlie these biases (Anderson, Laurent, & Yantis, 2014; Hickey & Peelen, 2015), but it is not known how these interactions occur, or which regions play a necessary role. These attentional effects are thought to potentially reflect the activation of an 'approach system,' dependent on incentive salience signals, posssibly originating from midbrain dopamine neurons (Anderson, 2013; Berridge & Robinson, 1998; Ikemoto & Panksepp, 1999). Notably, dopaminergic projections are relatively sparse in visual cortex (Berger, Trottier, Verney, Gaspar, & Alvarez, 1988), and therefore attentional effects in these visual areas might depend on mediating brain areas, where there are convergent connections between dopamine neurons and sensory regions (Pessoa, 2015). Anderson et

al. (2014) suggested that direct connections between cortical visual regions and the tail of the caudate, could mediate the influence of value on attention. However, this study only observed corticostriatal involvement in value-based attentional bias after extensive training, where value associations may have become deeply engrained and habit-like.

The small lesion literature on this topic points to the involvement of the ventromedial frontal lobe (VMF) in mediating attention based on feedback or emotional relevance. A case study found that the saccadic reaction times of a patient with bilateral VMF damage were insensitive to feedback (Hodgson et al., 2002). Another study found that an event-related potential associated with orienting attention in response to emotional distractors was reduced in patients with VMF damage (Hartikainen, Ogawa, & Knight, 2012). Other work examining the effects of reward associations on attentional event-related potentials and magnetic waves in healthy subjects have suggested that behavioral effects of reward association on selective attention depend on the anterior cingulate cortex (ACC), though these studies came to different conclusions regarding the mechanism involved (Buschschulte et al., 2014; Hickey et al., 2010a). How these frontal regions might influence attentional selection is also unclear: these biases could depend on direct connections with visual areas, or may be mediated indirectly through lateral PFC (Cisek & Kalaska, 2010), or intermediary subcortical structures (Pessoa, 2015).

Attention during value-based learning

Neurobiological explanations of associative learning have largely focused on mechanisms derived from computational frameworks like that described by Rescorla and Wagner (1972). Notably, dopaminergic neurons in the midbrain have been shown to display firing properties resembling positive and negative reward prediction errors

(Schultz, Dayan, & Montague, 1997), a signal anticipated by this account. While elegant and useful in pared down experimental settings, this model fails when confronted with more ecologically valid environments where stimuli have multiple dimensions (i.e. are composed of multiple features, like shape, color and texture), each of which may be predictive of feedback (Sutton & Barto, 1998; Wilson & Niv, 2012).

In environments with multi-dimensional stimuli, or with multiple potentially predictive cues, attention influences which stimulus-outcome relationships are learned, and therefore, which options are approached or avoided in the future. Pavlov (1927) showed that the physical saliency of a cue could dictate the strength of learning by presenting dogs with food rewards preceded by two simultaneous cues of different (e.g. loud and soft tones). When later presented with each conditioned stimulus alone, the salient stimulus evoked a much more robust salivary response, indicating that this stimulus 'overshadowed' learning about its weaker counterpart. While this phenomenon emphasizes the effects of bottom-up, stimulus-driven attention on learning, subsequent work has demonstrated that attention can also help select between potential predictors of feedback to guide learning. Attentional accounts of learning argue that the attentional priority of a cue is determined by its predictive value (Pearce & Mackintosh, 2010), its similarity to other reward associated cues (Mackintosh, 1975), and by its physical salience, as in Pavlov's study (Mackintosh, 1976). Experimental designs that emphasize the predictive value of some cues over others, such as blocking or highlighting, can produce seemingly irrational learning biases as attention is directed toward apparently predictive cues, influencing stimulus-outcome attribution (Kruschke, 2003).

Recent neuroimaging studies have suggested potential regions mediating this interaction between attention and associative learning. Lateral PFC and parietal regions are engaged when subjects are learning about the predictive value of stimulus dimensions (Niv et al., 2015). Other work has found that value-related hemodynamic activity within vmPFC is selective for option attributes that are currently relevant to a choice at hand (Hunt, Dolan, & Behrens, 2014; Lim et al., 2013), and that the representation of irrelevant option values in this region can predict the bias these distractors exert on choice behavior (Chau, Kolling, Hunt, Walton, & Rushworth, 2014). Deficits in credit assignment found in monkeys with damage to lateral OFC, or VLPFC, may depend on a role for this region in selecting stimulus features based on their current relevancy (Walton, Chau, & Kennerley, 2015). The amygdala is also suspected to play a key role in coding 'surprise' signals (i.e. an unsigned prediction error) during learning, potentially helping to modulate the attentional priority of cues (Esber & Holland, 2014; Roesch, Esber, Li, Daw, & Schoenbaum, 2012). Thus, recent work argues that these regions are involved in different aspects of attentional control during associative learning. Lesion evidence in monkeys and humans also suggest that both the amygdala and OFC are involved in associative learning tasks where it may be necessary to engage attentional mechanisms to select predictive cues (Bechara, Damasio, Damasio, & Lee, 1999; Murray, 2007; Tsuchida et al., 2010; Wellman, Gale, & Malkova, 2005).

Effects of attention on value-based choice

Selective attention also affects how we interact with our decision environment. In particular, attention can help select the subset of features or options that we engage with in the process of making a choice. Rather than a rational, holistic comparison of subjective

value, our choices more often appear to arise from a pared down and heavily filtered version of the complete decision space (Payne et al., 1993).

A number of recent studies reinforce this view of decision-making, demonstrating that attention influences choice behavior in a number of settings. For example, subjects are more likely to choose options that are visually more salient (i.e. visually higher contrast or luminance) than competing options (Milosavljevic, Navalpakkam, Koch, & Rangel, 2012; Towal, Mormann, & Koch, 2013). These effects, while small, are significant. Notably, models that combine information about salience and reward value explain choice behavior better than accounts that assume decisions arise from a purely rational comparison of option values (Navalpakkam, Koch, Rangel, & Perona, 2010).

Choice behavior can also be influenced by visual fixations. Options that are fixated longer are chosen more often that would be expected based on their subjective value alone (Krajbich, Armel, & Rangel, 2010; Krajbich & Rangel, 2011). This decision bias is present even when fixation times are experimentally manipulated (Armel, Beaumel, & Rangel, 2008; Shimojo, Simion, Shimojo, & Scheier, 2003), indicating that this bias does not simply reflect a correlation of visual fixations with manual option selection. Mechanistically, Krajbich et al. (2010) have proposed that the values of options outside of the current locus of fixation are discounted during the comparison process, resulting in a bias toward choosing options with a greater fixation advantage.

The neural bases of these attentional biases during choice are not well understood. Lim, O'Doherty, and Rangel (2011) showed that the location of visual fixations affects hemodynamic correlates of option value comparison in vmPFC and the ventral striatum, arguing that the value comparison process is dependent of overt changes in visual

attention. As mentioned above, other work has shown that value comparison signals within vmPFC reflect current attentional biases based on the relevance of option features (Hunt et al., 2014; Lim et al., 2013), supporting this view. VMF lesions also disrupt normal exploration of option features during value-based choice, further arguing that this region has some role in adaptively selecting stimulus features when comparing decision options (Fellows, 2006). However, the critical contribution of this region for mediating the influence of attention in choice behavior, if any, is unknown.

General methodology of lesion studies

This thesis tests the necessary contributions of frontal lobe sub-regions to value-based attention and choice in a large group of frontal lobe damaged patients. Before describing this work, it is necessary to first review the lesion method itself. Historically, group lesion studies in human patients have had major impact on the development of cognitive neuroscience. In some instances, even single cases have had a profound role in highlighting important brain-behavior relationships (e.g. Adolphs et al., 2005; Eslinger & Damasio, 1985; Milner, Corkin, & Teuber, 1968). For the greater part, these contributions have largely been in demonstrating dissociable behavioral deficits related to localized damage. With the advent of neuroimaging, contemporary cognitive neuroscience now heavily emphasizes network approaches and *in vivo* correlative measures of brain activity that can be extracted from these measures. However, this reliance on imaging can be dangerous, as cognitive neuroscience theory becomes less grounded in causal evidence. In this context, studies of focal lesion patients have a critical role, providing information through loss of function testing that can test predictions derived from human neuroimaging, as well as analogous lesion studies in animal models. Thus, these

approaches have complimentary roles in adjudicating between structure-function hypotheses (Fellows et al., 2005; Rorden & Karnath, 2004). The following section will review the general methodological considerations for human lesion studies before concluding with a general description of the approach taken in this thesis.

Methodological approaches to human lesion studies

Behavioral studies of the effects of brain lesions in humans can be broadly classified as following two methodological approaches. Behavior-based studies group patients based on the presence or absence of a behavioral impairment, testing if deficits are systematically related to damage to any particular brain area. In this approach, structure-function relationships are tested without necessarily specifying *a priori* hypotheses regarding the consequences of damage to any particular region, which may be an advantage for exploratory purposes. However, this method has several limitations. Categorizing patients as 'impaired' or 'unimpaired' may not be trivial. Even when clear criteria for impairment are established, reducing variance in patient behavior to a binary variable risks losing important information about task performance. Additionally, the exploratory nature of this approach limits the strength of the conclusions that can be made from this type of evidence. More recent analysis techniques have also largely supplanted this approach, as will be reviewed below. For these reasons, this method will not be further considered here.

In contrast, lesion-based studies compare groups of patients defined by the anatomical area affected by the damage. This method tests for differences in behavior between structurally defined lesion groups, and between these groups and matched, healthy subjects. The divisions of these groups can either be established based on anatomical landmarks, or in some variations, a particular ROI defined using an atlas (e.g.

Brodmann areas), or coordinates from imaging studies. This method is thus ideal for testing *a priori* structure-function hypotheses along broad anatomical divisions, or sometimes within more precise anatomical substrates. However, lesions within a group of human patients are rarely consistent or contained within a neatly defined brain area. Thus, this method is usually limited by low anatomical specificity.

Voxel-based lesion symptom mapping (VLSM) is a more recently developed approach that does not require any prior grouping of lesion patients to examine structure-function relationships (Bates et al., 2003). This method instead takes advantage of lesion tracings registered to a standard three-dimensional brain space, formally testing where behavioral deficits are associated with damage at a voxel-wise level. This method can therefore test for deficits with greater anatomical granularity than traditional lesion-based approaches and does not require binary categorization of patients based on impairments, as in behavior-based approaches. However, this method requires reduction of behavioral results to a single variable, potentially losing relevant information. VLSM also suffers from low power and require a large sample of patients with adequate lesion coverage to be used effectively (Kimberg, Coslett, & Schwartz, 2007). Additionally, lesion damage is non-random, as damage usually occurs in certain patterns that relate to the underlying etiology. For example, lesions due to ischemic stroke follow the brain's vascular supply, with some branches more likely to be affected than others. These common patterns of damage also result in covariance in subjects' lesions, particularly when patients have a similar etiology. For example, ischemic stroke in the middle cerebral artery may affect VLPFC, while also frequently affecting the insula and parietal and temporal perisylvian cortex. As a result, VLSM may detect artifactual associations between frequently damaged voxels and

behavioral deficits that are in reality related to damage in a less frequently affected region (Mah, Husain, Rees, & Nachev, 2014). This issue may be somewhat mitigated by the inclusion of patients with diverse etiologies and distinct patterns of damage. Greater diversity in etiology can thus reduce the covariance in the voxels affected by different lesions, and improve the anatomical specificity of VLSM analysis.

Lesion- or ROI-based methods and VLSM provide qualitatively different information. Recent studies have made use of the complimentary strengths of these methods, arguing that they may be more effective when combined than when used separately (Coulthard, Nachev, & Husain, 2008; Tsuchida & Fellows, 2009). This hybrid approach allows for more in-depth and better-powered comparisons of behavior between groups, while also testing for deficits with greater regional specificity using VLSM.

Lesion classification and registration

Comparison of lesions across groups of patients requires the area of damage to be segmented and registered to a common brain space. In the past, lesions were manually drawn onto brain templates based on surgeons' estimates of the damage, though the true lesion extent could only be obtained post mortem. Improvements in medical imaging now provide more detailed, albeit still incomplete, representations of the lesion through computerized tomography (CT) or magnetic resonance imaging (MRI).

In many studies, the lesion is segmented and registered to a common brain space manually by a neurologist or radiologist with expertise in interpreting these scans. This approach has limitations: it requires investment of time and expertise and may be subject to idiosyncratic biases in classifying what tissue is, and is not, damaged. Automated tools have been developed to segment these images based on the detection of deformations or

outliers, and register them to a common space (e.g. Crinion et al., 2007; Mah, Jager, Kennard, Husain, & Nachev, 2014). However, these methods may not be feasible for use with CT scans and some clinical MRIs, and may run into difficulties where distortions caused by the lesion can impede accurate registration, especially for large or bilateral lesions (Brett, Leff, Rorden, & Ashburner, 2001; Nachev, Coulthard, Jager, Kennard, & Husain, 2008). For these reasons, manual segmentation and registration remains a popular and commonly used approach (e.g. Gilboa, Alain, He, Stuss, & Moscovitch, 2009; Hartikainen et al., 2012; Levens et al., 2014; Manohar & Husain, 2016; Wolf, Philippi, Motzkin, Baskaya, & Koenigs, 2014).

Neuropsychological screening

Brain damage has effects on cognitive processes aside from functions of experimental interest. Premorbid functioning also differs between patients, as would be expected in any heterogeneous population sample. Neuropsychological screening tools can help identify these impairments and individual differences, and are therefore of use in addressing possible confounds and alternative explanations for behavioral deficits. However, the extensiveness of this screening is constrained by pragmatic factors, particularly the investment of time and effort on the part of the patient and experimenter (Fellows, Stark, Berg, & Chatterjee, 2008).

Overview of the methods used in this thesis

All three studies in this thesis used similar basic methods. Patients with focal frontal lobe damage and age and education matched, healthy control subjects were administered a series of computerized cognitive tests. Patients were recruited from research registries at

McGill University and the University of Pennsylvania and their lesions registered to a common brain space. Behavioral tasks were based on existing literature from studies in healthy normal individuals, and lesion studies in humans and non-human primates. In each study, we took a hybrid approach to testing the effects of damage, comparing behavior in patients first using *a priori* ROI methods, and then probing for more anatomically specific deficits using VLSM. Neurologists at the two testing sites (L.K.F at McGill University) or (A.C. at the University of Pennsylvania) completed manual segmentation and registration of patients' lesions to MNI space. Both neurologists were experienced in lesion methods and interpreting clinical scans, and were blind to the patients' performance. All patients were given a brief battery of screening tests to assess a range of basic cognitive functions prior to experimental testing.

Specific aims of the thesis

The work reviewed above describes the contributions of frontal lobe sub-regions to goal-directed selective attention and value-based decision-making. However, relatively little is known about the neural mechanisms underlying the interaction between selective attention and associative learning, or value-based decision-making. The central aim of this thesis was to examine the critical role of the frontal lobes in influencing value-based choice and learning through attentional mechanisms.

In the next three chapters, I will describe the results of the thesis work addressing this aim, testing a series of specific experimental questions. First, I examined the effects of frontal lobe damage on directing attention to reward-predictive stimulus features in a visual search task. In the second study, I assessed the contributions of frontal sub-regions to attributing reward feedback within an associative learning task where options were

comprised of multiple stimulus dimensions. The last study examined the effects of frontal lobe damage on the influence of fixations on value-based choice between naturalistic stimuli.

This work actively bridges attentional accounts of frontal lobe function with current research investigating the role of this region in decision behavior. By bringing these approaches together, this thesis establishes a starting point for understanding the necessary contributions of the frontal lobes in the interaction between top-down control of selective attention and motivated behavior. Here, causal evidence is provided for the distinct, and necessary, roles of frontal lobe sub-regions in these processes. This investigation has relevance for developing a mechanistic understanding of normal decision behavior, and potentially how these processes may go awry in psychiatric or neurological disorders.

Chapter 2: Ventromedial frontal damage reduces reward priming of attention

Preface

Lesion evidence in humans and monkeys has implicated the ventromedial frontal lobe in learning dynamic stimulus-reward relationships (Berlin, Rolls, & Kischka, 2004; Fellows & Farah, 2003; B. Jones & Mishkin, 1972). However, the basis of these deficits is not well understood. In this first study, published in The Journal of Neuroscience, we tested the hypothesis that damage to this region reduces attention to stimulus features that are predictive of reward. We investigated the effects of frontal lobe damage on attentional priming by stimulus features incidentally associated with rewards during a visual search task. Damage to the ventromedial frontal lobe, but not other frontal sub-regions, was found to reduce attentional priming by reward-predictive features. We suggest this region may have a role in guiding attention to reward-predictive stimuli, which may be mechanistically related to the contributions of this region in learning stimulus-reward relationships.

Ventromedial frontal cortex is critical for guiding attention to reward-predictive visual features in humans*

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Abstract

Adaptively interacting with our environment requires extracting information that will allow us to successfully predict reward. This can be a challenge, particularly when there are many candidate cues, and when rewards are probabilistic. Recent work has demonstrated that visual attention is allocated to stimulus features that have been associated with reward on previous trials. The ventromedial frontal lobe (VMF) has been implicated in learning in dynamic environments of this kind, but the mechanism by which this region influences this process is not clear. Here, we hypothesized that VMF plays a critical role in guiding attention to reward-predictive stimulus features based on feedback. We tested the effects of VMF damage in human subjects on a visual search task where subjects were primed to attend to task-irrelevant colors associated with different levels of reward, incidental to the search task. Consistent with prior work, we found that distractors had a greater influence on reaction time when they appeared in colors associated with high reward in the previous trial, compared to colors associated with low reward, in healthy control subjects, and patients with prefrontal damage sparing VMF. However, this reward modulation of attentional priming was absent in patients with VMF damage. Thus, intact VMF is necessary for directing attention based on experience with cue-reward associations. We suggest that this region plays a role in selecting reward predictive cues to facilitate future learning.

Introduction

From cafeterias to speed dating services, we are often called upon to make decisions based on complex and noisy information. Selective attention allows us to filter the external world and focus on what matters, such as cues that predict rewards (Anderson, Laurent, & Yantis, 2011a; Anderson et al., 2011b; Della Libera & Chelazzi, 2006, 2009b; Hickey et al., 2010a; Hickey, Chelazzi, & Theeuwes, 2010b; Kiss et al., 2009; Kristjansson et al., 2010). This reward-related attentional tuning might reflect an adaptive process, highlighting features based on their predictive value, which will in turn guide future learning (Gottlieb, 2012; Mackintosh, 1975; Navalpakkam et al., 2010; Wilson & Niv, 2012). In this way, attention and associative learning are inextricably linked, with attention adjusting the gain on stimuli that potentially predict rewards.

Several lines of evidence support a role for the ventromedial frontal lobe (VMF) in value-based learning. Lesions to this region in patients and animal models impair learning about dynamic stimulus-reward associations (Berlin et al., 2004; Tsuchida et al., 2010; Walton et al., 2010). Imaging and monkey electrophysiology studies support these findings, showing that VMF activity encodes the relative value of options (Boorman, Behrens, Woolrich, & Rushworth, 2009; Kable & Glimcher, 2007; Kennerley et al., 2011; Padoa-Schioppa & Assad, 2006; Thorpe et al., 1983). However, the mechanism by which these stimulus value signals influence behavior remains unclear.

VMF might play a role in learning the reward-predicting features of the environment: guiding attention to stimulus features previously associated with rewards. This region is robustly connected with sub-cortical regions involved in reward processing (Carmichael & Price, 1995a; Cavada, Company, Tejedor, Cruz-Rizzolo, & Reinoso-Suarez,

2000; Eblen & Graybiel, 1995; Price, 2007), and has reciprocal connections with diverse sensory systems (Carmichael & Price, 1995b). Hence, VMF is well situated for integrating value information with perceptual representations of stimuli (Barbas et al., 2011). Recent work has shown that functional connectivity between VMF and higher-order sensory regions is dynamically modulated as a function of the behavioral relevance of information processed in these areas (Lim et al., 2013; Philiastides et al., 2010). VMF might therefore play a role in prioritizing features that carry value information, contributing to the construction of an attentional set adapted to the current environment.

We hypothesized that VMF plays a necessary role in using feedback to guide attention to reward-predictive stimulus features. We asked patients with prefrontal damage and healthy, demographically-matched controls to complete a visual search task that induced trial-by-trial priming of a particular stimulus feature (color) based on its association with a high or low probability of a large reward, incidental to the instructed task. We expected that distractors that were primed by the high reward color in the previous trial would capture attention more than the low reward color in control subjects and patients with damage outside of VMF. We predicted that these color-reward associations would have less influence on attention in VMF damaged subjects.

Materials and Methods

Subjects

Twenty-four patients with focal lesions involving the frontal lobes were recruited from the Cognitive Neuroscience Research Registry at McGill University, and nine patients were recruited from the Center for Cognitive Neuroscience at the University of Pennsylvania (Fellows et al., 2008). They were eligible if they had a fixed lesion primarily

affecting the frontal lobes. One DMF patient, two LF patients and one VMF patient found the task too difficult and did not complete the experiment. One patient with VMF damage was removed from the study after it was found that she had extremely low accuracy for trials where the target was on the right side of the screen. Removing this patient did not affect the main result: indeed, this patient showed a larger priming effect for the low reward color than the high reward color. Another patient was removed when it was found that the boundaries of her lesion could not be accurately established. The final sample included 27 patients with frontal lobe damage, 14 males and 13 females.

Patients were tested a minimum of 6 months after the injury (median, 6.4 years after; range, 8 months to 48.1 years). Damage to DMF was caused by tumor resection in 8 cases, aneurysm in 1 case, ischemic stroke in 1 case and hemorrhagic stroke in 1 case. Damage to LF was caused by tumor resection in 3 cases, ischemic stroke in 3 cases and hemorrhagic stroke in 1 case. Damage to VMF was caused by tumor resection in 4 cases, hemorrhagic stroke in 3 cases and aneurysm in 2 cases. Eleven patients were taking one or more psychoactive medications, most commonly an anticonvulsant or anti-depressant.

Patients were separated into groups *a priori* based on the location of their damage, assessed on their most recent MR or CT imaging by a neurologist experienced with neuroimaging and blind to task performance. Patients with lesions primarily affecting VMF were identified first, as the primary region-of-interest. The remaining patients were then subdivided further into dorsomedial frontal (DMF) and lateral frontal (LF) groups. Patients' lesions were manually registered to a common brain space (MNI brain) by neurologists at the research sites, blind to task performance, to allow overlap images to be generated, and to support voxel-based lesion-symptom mapping. The overlap images for the three

anatomically defined groups are shown in Figure 2.1.

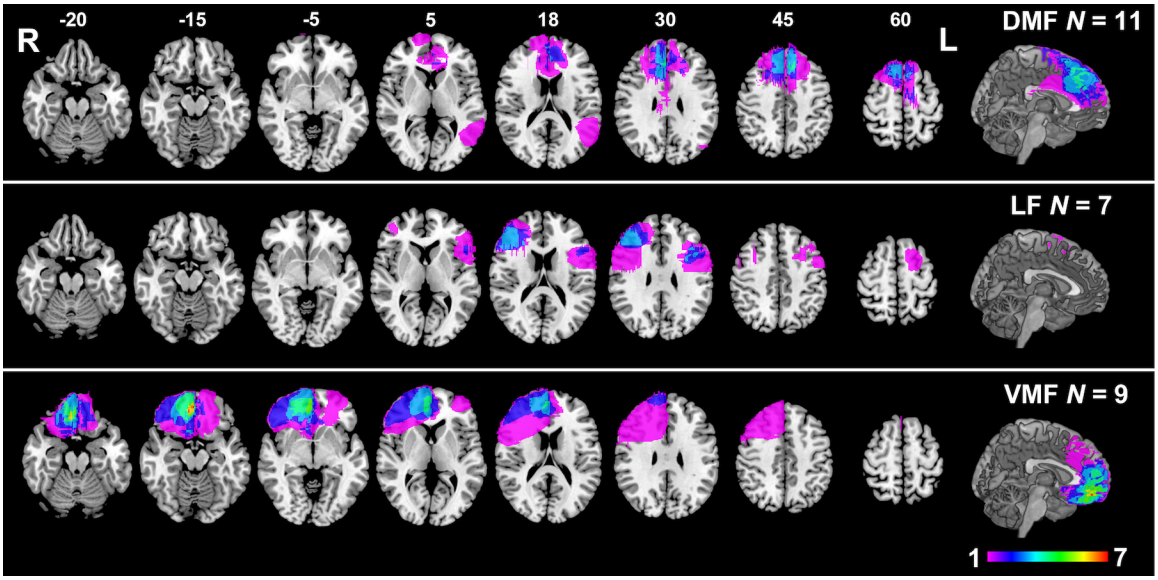

Figure 2.1. Representative axial slices and mid-sagittal view of the MNI brain showing the extent of lesion overlap in the dorsomedial frontal (DMF, top row), lateral frontal (LF, middle row) and ventromedial frontal (VMF, bottom row) groups. Numbers above slices indicate z- coordinates of axial slices in MNI space. Colors indicate extent of lesion overlap, as indicated by the color scale. R, Right; L, Left.

Age- and education-matched healthy control subjects (N =21) were recruited through local advertisement in Montreal, including 7 males and 14 females. They were free of neurological or psychiatric disease and were not taking any psychoactive medication. They were excluded if they scored 26 or less on the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005). Mean performance on this test was 28.0, *SD* = 1.5. All subjects provided written informed consent in accordance with the Declaration of Helsinki and were compensated with a nominal fee for their time. The study protocol was approved by the institutional review boards of both participating centers.

Apparatus

All tests were programmed using E-Prime 1.2 (Psychology Software Tools, Inc., Pittsburgh, PA, USA). Seventeen patients and all 21 controls were tested at the Montreal

Neurological Institute. They saw stimuli presented on a 19-inch monitor (Dell Inc., Round Rock, TX, USA) and responded using the up and down arrow keys on a standard PS/2 keyboard (Dell Inc., Round Rock, TX, USA). Ten patients tested at the University of Pennsylvania, or in home visits in the greater Philadelphia and Montreal areas, performed the experiment on a 13.5 inch laptop (Fujitsu Ltd., Tokyo, Japan) and used the up and down arrow keys of the laptop keyboard for their responses.

Procedure

Subjects completed a visual search task where they were asked to report the orientation of a 'T' shaped target character (pointing up or down) on each trial. This task was similar to those used in previous studies examining the effect of rewards on visual attention (e.g. Hickey et al., 2010a; Kristjansson et al., 2010), with subjects primed to search for task-irrelevant features by associating those features with higher rewards incidental to the primary task.

The task is detailed in Figure 2.2. The task consisted of four blocks of 144 trials each. On each trial, subjects first saw a central fixation cross for 750 ms, followed by two square arrays made up of 8 white 'T' shaped distractor characters (randomly pointing up or down) on the left and right of the screen for 500 ms. Subjects had to find a colored target 'T' (randomly pink or orange on each trial) that was embedded in the center of either the left or right array, and report its orientation via key press (pressing the up arrow key if the target was upright, or the down arrow key if it was inverted). Opposite the target character was a salient distractor (a 'T' turned 90 degrees, facing left or right) that was also colored (pink if the target was orange, or vice versa), which subjects were instructed to ignore. The search array was masked by scrambled images of the items in the search array. After 400

ms, the mask was removed and subjects saw the fixation cross for another 600 ms before the trial ended and feedback was displayed for 500 ms. Subjects could respond at any point in the 1500 ms period from the presentation of the search array to the presentation of feedback. A blank gray screen was shown for 700 ms between the termination of feedback presentation and the next fixation cross. Subjects were explicitly instructed that they could still respond after the search array had disappeared, until they saw feedback. Trials were balanced so that the target character appeared in both colors equally often in each block, as well as equally often on the left or right side of the screen, and oriented upright or inverted.

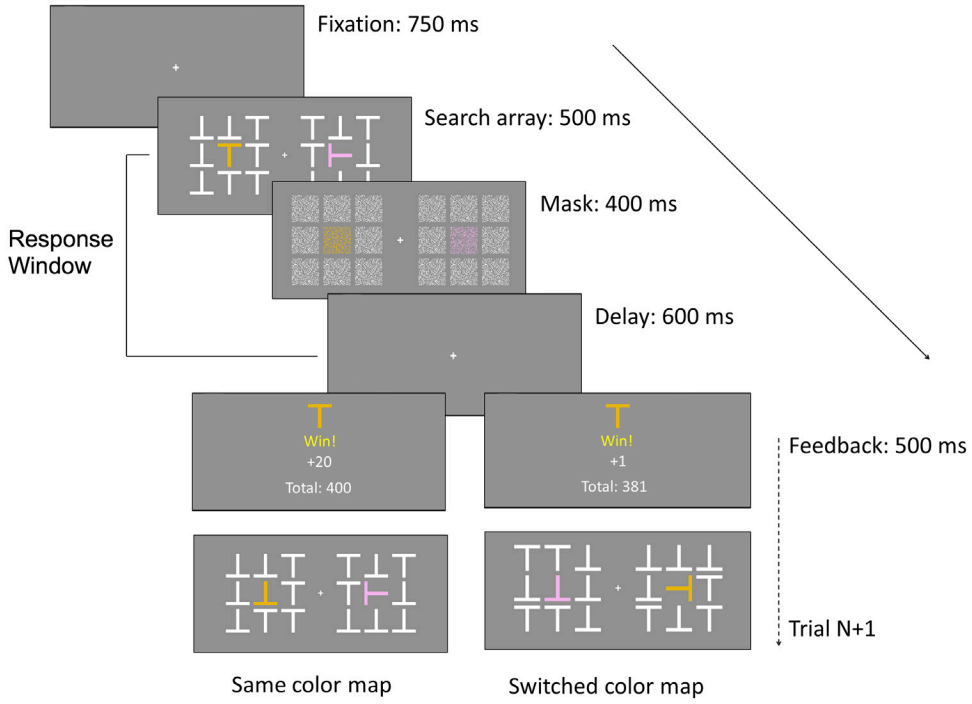

Figure 2.2. Task design. In each trial, subjects saw a search array composed of white 'T' shapes (randomly oriented up or down) with an embedded colored target 'T' that randomly appeared on the left or right side of the screen. Subjects reported the orientation of the target (up or down) through key press while ignoring a salient, perpendicular, colored, distractor on the opposite side of the screen. After 500 ms, the search array was replaced with a mask for 400 ms, followed by 600 ms delay. Subjects could respond at any point in this 1500 ms period from the presentation of the search array to the termination of the delay screen. Subjects then saw a feedback screen for 500 ms, with the likelihood of high or low magnitude reward determined by the target color (counterbalanced across subjects). In the following trial (N+1), the colors of the target and salient distractor would randomly either remain the same, or switch.

On correct trials, the feedback screen showed the target and the number of points earned in the trial, as well as a running count of the total points earned in the block. Subjects earned points for correct responses within the allotted response window. The number of points earned depended probabilistically on the color of the target. For each subject, one color yielded a high reward (20 points) on 80% of trials, and a low reward (1 point) the rest of the time, while the other color had the reverse reward association. Feedback was paired with a 500 ms high or low pitched 'ding' sound to indicate the size of

the reward. The colors associated with a greater or lesser chance of a high reward (referred to henceforth as the 'high reward' and 'low reward' colors) were counterbalanced across subjects in each group. Critically, the color of the target and salient distractor could randomly stay the same ('same color') or switch ('switched color') between trials. This manipulation was intended to elicit a 'priming of pop-out' effect where subjects take longer to detect the target on switch trials (Maljkovic & Nakayama, 1994). Ultimately, we were interested in whether this priming effect would be larger for trials where the distractor appeared in the high reward color compared to trials where it appeared in the low reward color.

On trials where subjects responded too late or incorrectly, the feedback simply showed a red zero for the points earned, and the total points earned in the block. This feedback screen was paired with a 500 ms 'buzz' sound to alert subjects to their mistakes. Subjects were told that points would be awarded for responding quickly and accurately, and that their points would be converted into a monetary bonus added to their base compensation for their time and inconvenience. They were not instructed about the color-reward associations.

Before the main experiment, subjects completed a practice version of the task. This practice task was identical to the main experiment, except that the target and salient distractor were both black, rather than colored, and subjects did not earn points for correct responses. Instead, subjects simply saw the words 'correct' or 'error' as feedback on correct trials or errors and late responses. Feedback was not accompanied by any sounds during the practice. The practice block consisted of 72 trials. Most subjects only required one

block of practice, though a few patients and controls completed an extra block to ensure they had adequately learned how to perform the task.

Data analysis

We were primarily interested in testing whether VMF damage, and not other frontal damage, reduced priming of attention to highly rewarded colors. We thus focused on trials where subjects made consecutive correct responses and therefore received high or low reward in the previous trial. We limited our analysis to trials where the magnitude of reward received in the previous trial was congruent with the reward level associated with the color of the target. We also removed outlier trials by rejecting trials where reaction time (RT) was more than two standard deviations higher than each subject's mean RT (M = 4.6%, SD =1.0% of trials per subject). After filtering the data, there were an average of 102.0, SD = 14.6 trials per condition-subject available for the main analysis of reward priming effects. Unfortunately, there were not enough trials per condition to reliably analyze reward priming effects in trials where subjects had received incongruent rewards on the previous trial (M = 17.7, SD = 4.2 trials per condition-subject). To reduce variance due to idiosyncratic differences between individuals in RT, we converted RTs to Z-scores based on the mean and standard deviation of each subject's RTs in the trials under analysis.

Statistical analysis

Demographic variables for patients and controls were compared using uncorrected, unpaired *t*-tests, or Mann-Whitney U-tests where parametric tests were not appropriate. Neuropsychological screening scores were compared between groups using one-way ANOVA's, or Kruskal-Wallis non-parametric tests. Wilcoxon signed-rank tests were used to compare circle cancellation misses for the left and right side of the screen within each

group to test for hemispatial neglect. Further neglect screening was carried out with a classic Posner spatial cueing task (Posner, 1980), which was tested with a two-way mixed measures ANOVA, with a factor for group status and target location (left or right, or contra- or ipsilesional).

Differences in task performance between groups on the visual search task (proportion of trials correct, incorrect or missed) were evaluated using a chi-squared test for independence. RT and arcsine transformed accuracy for ipsi- and contralesional targets were compared within patients with unilateral damage using two-way mixed measures ANOVAs, with separate factors for group status and target side (ipsi- or contralesional).

Priming effects of reward associated colors on normalized RT and arcsine transformed accuracy were tested using a three-way mixed measures ANOVA. Group status was treated as a between-subjects factor, and target and distractor color consistency (same or switch) and distractor color value association (high or low) as the two within-subjects factors. Similarly, we also evaluated the effects of rewards on priming of position with another three-way mixed measures ANOVA. Group status was treated as a between-subjects factor, with target and distractor position consistency (same or switch), and the reward level of the previous trial (high or low) as within-subject factors. Reward priming, as measured by the interaction of color consistency and distractor color value, was computed in the first half and the last half of the experiment and the interaction of experiment period and group on this priming effect was analyzed using a two-way ANOVA.

Behavior-based lesion analysis

The Non-Parametric Mapping (NPM, version June 6, 2013) software (freely available at www.mccauslandcenter.sc.edu/mricro/npm/) was used for voxel-based lesion symptom

mapping (VLSM) analysis. The interaction effect (difference of the priming effect for high and low reward colors) was used as a continuous measure to test where decreased reward priming was associated with lesion damage. Voxel-wise comparisons between patients were carried out using non-parametric Brunner-Munzel (BM) tests (Brunner & Munzel, 2000) in all voxels where there were three or more patients with lesion damage. To control for multiple comparisons, a null distribution of BM *Z*-scores was calculated from the same dataset using permutation tests (3000 permutations) (Nichols & Holmes, 2002). This method provides an assumption free means of controlling for multiple comparisons that is also more powerful than commonly used corrections like the Bonferroni method (Kimberg et al., 2007). This test yielded a threshold of $Z > 3.21$ (for $p < 0.05$, corrected). Images of the results of this analysis were created using the software MRICron.

Results

Demographics and neuropsychological screening

Demographic and background information on controls and patient groups are provided in Table 2.1. There were no significant differences in age or education between controls and patient groups (Unpaired t-tests: t's ≤ 1.26, P's ≥ 0.2, uncorrected), or in lesion volume between different patient groups (Mann-Whitney U tests: z's ≤ 0.72, P's ≥ 0.5, uncorrected). Premorbid intelligence quotient was estimated using the American Nelson Reading Test (AMNART) (Grober & Sliwinski, 1991). AMNART IQ was significantly lower in the VMF group compared to controls (t (23) = 3.01, P = 0.006, uncorrected), though patients with LF or DMF damage were not different from controls (t's ≤ 1.62, P's ≥ 0.1, uncorrected), nor were patient groups different from each other (t's ≤ 1.02, P's ≥ 0.3, uncorrected). Scores on the BDI-II were also higher in all three patient groups relative to

controls (t's ≥ 2.46, P's ≤ 0.02, uncorrected), though there were no differences between the patient groups (t's ≤ 0.48, P's ≥ 0.6, uncorrected).

Table 2.1. Demographic information for controls and prefrontal patients. Values represent means with standard deviations in parentheses, except for lesion volume, where the median and range are provided.

Group	Age (years)	Sex (M/F)	Education (years)	BDI-II	AMNART IQ [a]	Lesion Volume (cc)
CTL (N=21)	61.6 (10.1)	7/14	15.7 (3.3)	4.6 (4.2)	119 (5)	-
DMF (N = 11)	59.3 (7.4)	5/5	14.0 (4.3)	11.4 (8.1)*	116 (11)	17 (3-49)
LF (N = 7)	60.4 (8.1)	3/4	14.0 (4.0)	9.7 (6.3)*	116 (8)	23 (9-37)
VMF (N = 9)	61.8 (11.3)	4/5	14.9 (6.0)	12.2 (7.3)*	110 (11)*	21 (10-192)

[a] Not all subjects were able to complete the AMNART. * $P < 0.05$, two-tailed t-test against control scores, uncorrected

Subjects also underwent screening for visual neglect to test spatial attention to the left or right hemifield. There was no significant difference in the frequency of missed targets on the left or right side of the screen for any lesion group in a circle cancellation task (Wilcoxon signed-rank tests: z's ≤ 1.34, P's ≥ 0.2). We also compared the difference in RT for detection of uncued and cued targets on the left and right side of the screen in a classic Posner spatial cueing task (Posner, 1980). We found no interaction between group status and target location ($F_{(3,44)} = 0.20$, $P = 0.9$), or any difference between left and right targets ($F_{(1,44)} = 0.11$, $P = 0.7$), or overall differences between groups ($F_{(3,44)} = 0.10$, $p = 0.9$) for this cueing effect. We examined if there were differences in this cueing effect for contra- or ipsilesional targets in 19 patients with unilateral damage (7 DMF, 7 LF and 5 VMF patients). Once again, there was no significant interaction between target location and group ($F_{(2,16)} = 1.15$, $p = 0.3$), target location ($F_{(1,16)} = 0.10$, $P = 0.7$), or group ($F_{(2,16)} = 0.94$, $P = 0.4$). Patients thus showed no evidence of hemispatial neglect.

Subjects also underwent brief neuropsychological screening to test cognitive functions that were not under study, but potentially affected by frontal lobe damage. There were no differences between patient groups in fluency tasks or backwards digit span (One-way ANOVAs: $F's_{(2,21)} \leq 1.12$, $P's \geq 0.3$). Results from these screening tests are summarized in Table 2.2.

Visual search task performance

In the main experiment, subjects completed a visual search task where they had to identify the orientation of a colored target that appeared opposite a salient, colored distractor on each trial. This task involved a 'priming of pop-out' manipulation (Maljkovic & Nakayama, 1994), where the color of the target and salient distractor would randomly remain the same, or switch, every trial. This manipulation causes an increase in RT for trials where colors switch compared to when they stay the same, which is thought to arise from an experience dependent priming of search for the features discriminating the target from distractors in previous trials (Becker, Folk, & Remington, 2013; Kristjansson & Campana, 2010). Critically, the color of the target in this task was predictive of a reward outcome on each trial, but irrelevant to the task (reporting the orientation of the target). Previous work using similar paradigms have found a larger priming effect for colors paired with high rewards compared to priming by colors paired with low rewards (Anderson et al., 2011a, 2011b; Hickey et al., 2010a, 2010b; Hickey, Chelazzi, & Theeuwes, 2011; Kristjansson et al., 2010).

Table 2.2. Performance on neuropsychological screening tests for controls and prefrontal patients. Values represent means with standard deviations in parentheses.

Group	Posner Cueing (Uncued-Cued) Left/Right (ms)	Circle cancellation % missed (Left/ Right)	Fluency - animals	Fluency - F	Backwards Digit Span Score
CTL (N=21)	57.2 (50.9) 53.8 (36.9)	- -	-	-	-
DMF (N=11)	54.6 (49.9) 56.0 (45.2)	1.0 (2.3) 1.8 (2.7)	17.6 (8.3) [a]	8.2 (4.4)	2.4 (1.1) [a]
LF (N=7)	51.2 (50.7) 55.7 (50.5)	0.3 (0.9) 1.1 (2.0)	20.4 (9.3)	11.7 (5.2)	3.3 (1.4)
VMF (N=9)	69.2 (45.8) 56.5 (51.2)	1.2 (1.9) 1.6 (2.3) [a]	17.6 (3.1) [a]	10.5 (5.3) [a]	3.0 (1.3) [a]

[a] Data missing from one patient in group.

We first assessed basic aspects of task performance, summarized in Table 2.3. We compared the percentage of correct responses, errors and missed responses (i.e. failure to respond by the deadline) between groups. There was a significant effect of group on performance ($\chi^2 = 630.04$ (6), $P < 0.001$). In general, PFC groups performed worse than control subjects, with the worst performance in the DMF group on average. However, all subjects responded correctly in more than 70% of trials. We next compared raw RT for correct responses between groups. There was a significant effect of group on RT ($F_{(3,44)} = 3.02$, $P = 0.04$), with post-hoc tests showing that VMF patients were significantly slower than controls (Tukey/Kramer test: $p < 0.05$), but no other significant group differences (P's > 0.05).

We also tested for differences in accuracy and RT for targets presented to the contra- or ipsilesional hemifield in patients with unilateral damage. There was no significant main effect of target side (F's $_{(1,16)} \leq 0.17$, $P \geq 0.7$), or group (F's $_{(2,16)} \leq 0.13$, $P \geq 0.9$), or any significant interactions between group and target side on accuracy and RT (F's

$_{(2,16)} \leq 1.94$, $P \geq 0.2$). These data are also summarized in Table 2.3. Thus, task performance appeared to be similar for contra- and ipsilesional targets.

Reward priming of color

We anticipated that subjects' RTs would be longer following trials where the colors of the target and salient distractor switched. We also expected this effect would be larger for controls and patients with damage outside of VMF when the salient distractor appeared in the high reward color compared to trials where it appeared in the low reward color. In contrast, we expected that VMF patients would show no difference in this priming effect for distractors in high or low reward colors.

Table 2.3. Basic task performance data for controls and prefrontal patient groups. Values represent the means with standard deviation in parentheses.

	All subjects				**Unilateral damage**	
Group	**% Misses**	**% Errors**	**% Correct**	**RT (ms)**	**% Correct (Contra- / Ipsilesional)**	**RT (ms) (Contra- / Ipsilesional)**
CTL (N=21)	0.3 (0.3)	2.6 (2.2)	97.1 (2.5)	654.8 (62.6)	-	-
DMF (N=11)	1.7 (2.3)	10.1 (6.8)	88.2 (8.1)	699.7 (78.7)	91.5 (7.7) 89.2 (8.8)	695.3 (96.8) 719.5 (72.4)
LF (N=7)	0.9 (1.4)	7.7 (3.5)	91.4 (4.1)	686.7 (68.2)	92.3 (3.5) 90.3 (5.6)	682.3 (83.0) 694.0 (74.4)
VMF (N=9)	2.1 (2.8)	5.8 (4.9)	92.0 (7.4)	736.7 (81.6)*	88.1 (13.6) 91.6 (5.8)	725.8 (92.4) 668.4 (46.1)

* $P < 0.05$, Tukey-Kramer post-hoc test against controls

Reaction times were analyzed in a three-way mixed measures ANOVA with factors for group status, color consistency (stay or switch) and distractor value (high or low) (Fig. 2.3a). Across all groups, there was a robust main effect of color consistency (Mixed measures ANOVA: $F_{(1,44)} = 26.77$, $P < 0.0001$), with higher RTs for switch trials than trials where colors remained the same. There was also a significant interaction between color consistency and distractor value across groups ($F_{(1,44)} = 6.18$, $P = 0.02$), with a larger color

priming effect for high reward distractors than low reward distractors. Critically, there was also a significant three-way interaction between group, color consistency and distractor value on RT ($F_{(3,44)} = 4.47$, $P = 0.008$). Post-hoc tests between groups on this interaction effect revealed that the reward priming effect for VMF patients was significantly lower than DMF and LF patients (Tukey/Kramer tests: P's < 0.05), even trending in the opposite direction from the other groups (i.e. a larger priming effect for the low reward color than the high reward color; Fig 2.3b). There were no significant main effects of distractor value ($F_{(1,44)} = 0.08$, $P = 0.8$), or group ($F_{(3,44)} = 0.92$ $P = 0.4$) on RT. Nor were there any significant interactions between group and distractor value ($F_{(3,44)} = 0.22$, $p = 0.9$), or between group and color consistency ($F_{(3,44)} = 1.92$, $P = 0.1$). Thus, reward priming of attention in VMF patients was reduced relative to the other groups.

The same pattern of results was seen when RT outliers were included. The three-way interaction between group, color consistency and reward priming was somewhat weaker, but still statistically significant (Mixed measures ANOVA: $F_{(3,44)} = 3.34$, $P = 0.03$). Post-hoc tests revealed significant differences in this interaction between the VMF group and controls, as well between VMF and LF damaged patients (Tukey/Kramer tests: P's < 0.05), but no other significant differences (P's > 0.05).

We also tested for any reward priming effects on accuracy, and if this effect differed between groups. (Fig 2.3c) There was a significant effect of group, with controls responding more accurately than PFC groups, as described earlier (Mixed measures ANOVA: $F_{(3,44)} = 9.73$, $P < 0.0001$). There was also a trend toward a main effect of color consistency ($F_{(1,44)} = 3.62$, $P = 0.06$), with lower accuracy on trials where the color switched compared to when it remained the same. There was no main effect of distractor value ($F_{(1,44)} = 0.08$, $P = 0.8$), nor

any interaction between distractor value and color consistency on accuracy ($F_{(1,44)} = 1.07$, $P = 0.3$). Similarly, the three-way interaction between group, distractor value and color consistency was not significant ($F_{(3,44)} = 1.34$, $P = 0.3$). There was no interaction between color consistency and group on accuracy ($F_{(3,44)} = 0.85$, $P = 0.5$), though there was a trend toward an interaction between distractor value and group ($F_{(3,44)} = 2.52$, $P = 0.07$), with most groups showing a slight improvement in accuracy on high versus low distractor value trials, with the exception of the DMF group.

We next examined whether reward priming of attention changed over the course of the task by comparing the interaction effect of distractor value and color consistency in the first and last half of the experiment (Fig 2.3d). Specifically, we were interested in whether the VMF group simply learned reward associations at a slower rate, and were therefore delayed in showing reward priming. There was a significant main effect of group (Mixed measures ANOVA: $F_{(3,44)} = 2.98$, $P = 0.04$), with lower reward priming in the VMF group compared to other PFC groups and controls. However, we found no main effect of experiment period ($F_{(1,44)} = 0.04$, $P = 0.8$), or interaction between the period of the experiment and group ($F_{(3,44)} = 0.46$, $P = 0.7$). These data indicate that decreased reward priming in the VMF group was consistent over the course of the experiment.

As the VMF group was also the slowest in responding during the task, we tested if there was any relationship between overall RT and the reward priming effect. A simple Pearson correlation between raw RT and the interaction effect of high and low reward color priming in the control group found no significant relationship ($r(19) = 0.02$, $P = 0.9$). Thus, differences in reward priming between groups were unlikely to be a consequence of response speed. We also examined if the reward priming effect depended on the colors

themselves (i.e. if reward priming was different when orange was associated with high reward versus pink). There was no significant difference in reward priming in control subjects between the two color conditions (Unpaired t-test: t (19) = 0.93, P = 0.4), indicating that both color-reward associations had equivalent effects on attention.

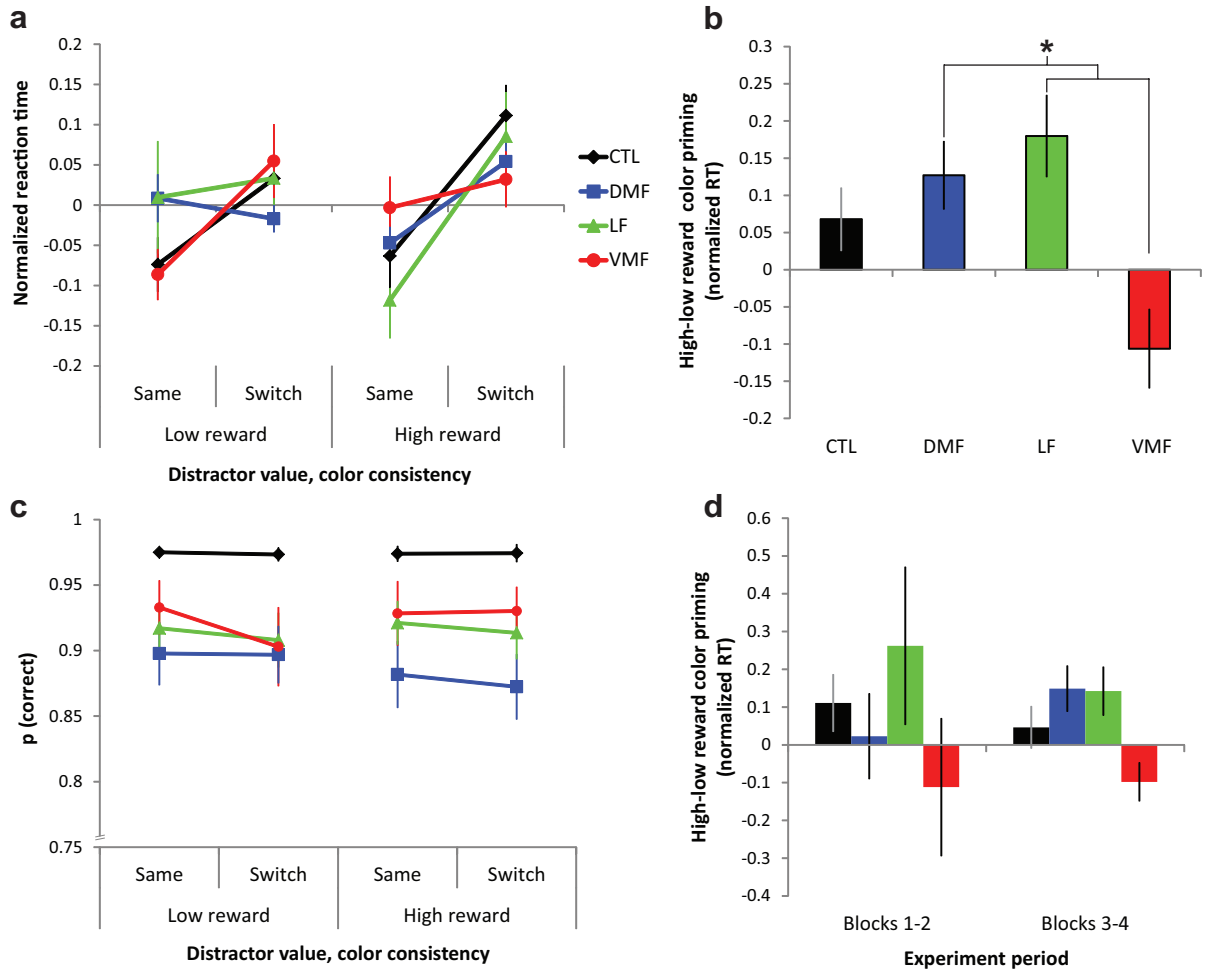

Figure 2.3. Effects of reward on color priming in each group. **a,** Normalized reaction times (RT) for target discrimination when the salient distractor color was associated with high or low magnitude reward, and when target and salient distractor colors remained the same or switched relative to the last trial . **b**, Difference in the priming effects for high and low reward colors on normalized RT (i.e. interaction effect from **a)**. **c**, Mean frequency of correct responses when salient distractor color was associated with high or low reward magnitude, and when target and salient distractor colors remained the same or switched. **d**, Interaction effect of color consistency and distractor color value on normalized RT in the first half of the experiment (blocks 1-2) and second half (blocks 3-4). Error bars indicate SEM. * P < 0.05, Tukey-Kramer post-hoc test.

Priming of position

The design of our experiment also included a 'priming of position' manipulation in that a target could randomly appear on the same, or opposite, side relative to the previous trial. Subjects are more efficient at detecting targets that appear in the same location compared to when the location changes, and are less efficient when targets appear where a distractor appeared on the previous trial (Kristjansson, Vuilleumier, Schwartz, Macaluso, & Driver, 2007; Maljkovic & Nakayama, 1996). Previous work has found that reward expectations modify spatial attention, leading to prioritization of locations associated with greater likelihood of reward (Chelazzi et al., 2014; Hickey, Chelazzi, & Theeuwes, 2014). While reward was not contingent on target location in this experiment, testing whether priming of position effects were modified by rewards provides an interesting control condition to examine if frontal groups or controls directed their attention based on spurious correlations between location and reward, in addition to the effects of consistent reward-color associations established over the course of the experiment.

We tested whether RT was affected by the change in target position from the last trial, and if this effect was influenced by the level of reward that subjects had received. There was a strong effect of change in target position ($F_{(1,44)} = 155.52$, $P < 0.0001$), with subjects taking longer to respond after a change of position compared to when the target appeared in the same location (Fig 2.4a). However, there was no significant interaction between change in target position and previous reward level, though there was a mild trend ($F_{(1,44)} = 2.81$, $P = 0.1$). The three-way interaction between group and the effect of previous reward on change of target position was also not significant ($F_{(3,44)} = 1.11$, $P = 0.4$, Fig 2.4b). Thus, reward priming effects did not just arise through fleeting associations based on the previous trial, but were strongest for the color feature that was informative

about rewards through consistent (albeit probabilistic) associations across the whole experiment. There was also a significant main effect of previous reward magnitude ($F_{(1,44)} = 6.75$, $P = 0.01$) and an interaction between previous reward magnitude and group ($F_{(3,44)} = 3.53$, $P = 0.02$). All groups, with the exception of the VMF-damaged group, tended to be slower to respond after a high reward compared to a low reward (mean (sd) normalized RT difference high-low, collapsed across position consistency: CTL: 0.01 (0.09), DMF: 0.07 (0.08), LF: 0.08 (0.07), VMF: -0.03 (.10)). There was no main effect of group ($F_{(3,44)} = 0.01$, $P = 0.9$).

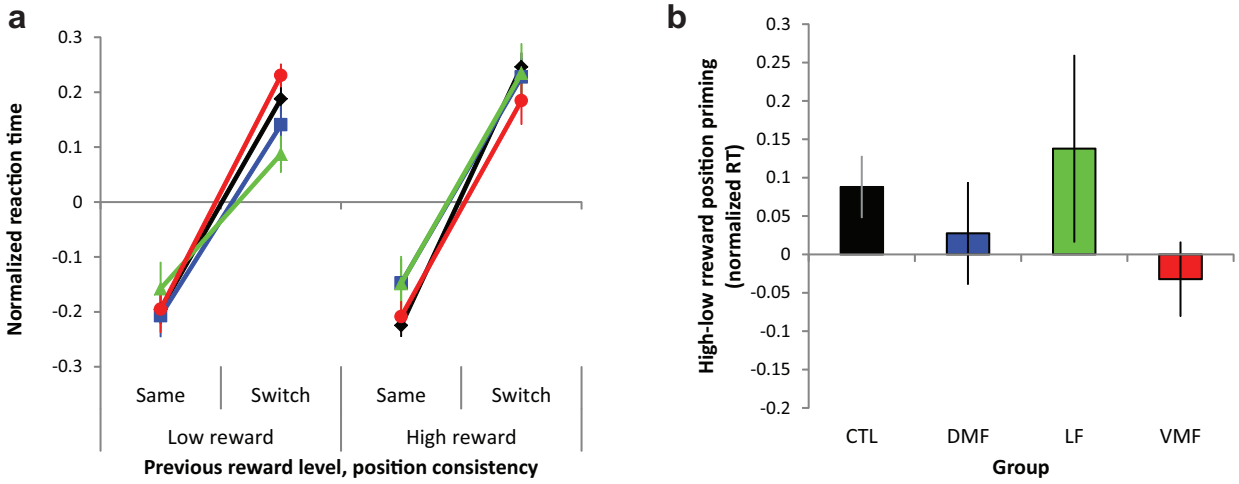

Figure 2.4. Effects of reward on position priming in each group. **a**, Normalized RT for target discrimination when subjects received either high or low magnitude reward in the last trial, and when target and salient distractor remained in the same position or switched. **b**, Difference in priming of position effect on normalized RT following high and low magnitude rewards. Error bars indicate SEM.

Voxel-based lesion symptom mapping

The above results argue for the critical involvement of VMF, and not of other PFC regions, in reward priming of attention during visual search. The region of interest approach can obscure the effects of damage that crosses the regional boundaries imposed *a priori*. Voxel-based lesion symptom mapping (VLSM) is an analytic approach that

overcomes this limitation, systematically testing the impact of damage at the voxel level (Bates et al., 2003; Rorden, Karnath, & Bonilha, 2007), although with greater power for detecting effects in regions with greater lesion overlap (Kimberg et al., 2007). We applied this method in a secondary analysis, including all voxels where at least three patients had damage (Coulthard et al., 2008; Haramati, Soroker, Dudai, & Levy, 2008; Tsuchida et al., 2010).

To test the effects of lesion damage on reward priming we used the interaction effect of distractor value and color map in the VLSM analysis (difference of priming by the high and low reward colors, Fig 2.3b). The non-parametric Brunner-Munzel test (Brunner & Munzel, 2000) was applied at all voxels with sufficient lesion overlap, and the threshold for statistical significance was determined using permutation testing to correct for multiple comparisons. Figure 2.5a shows the voxels where there was sufficient power to detect effects of lesion damage at the permutation corrected threshold for $P < 0.05$ ($Z > 3.21$) in this group of patients, as assessed by Wilcoxon rank-sum tests, as in Glascher et al. (2009). Colors indicate the maximum detectable Z score, representing the power for tests at each voxel. Voxels associated with a reduced, or reversed, priming effect for high versus low reward colors are shown in Fig 2.5b. Damage in right orbitofrontal cortex was most strongly related to the behavioral effect. The strongest statistical effects ($P < 0.05$) were in two small clusters of voxels, one in the right gyrus rectus (MNI: 4, 49, -16), and another more posterocentrally (MNI: 16, 19, -22) (Tzourio-Mazoyer et al., 2002). Testing the opposite effect (increased reward priming) with VLSM did not reveal any voxels that were above the permutation corrected criterion for statistical significance ($Z = 3.17$). However, there were two clusters of voxels above the uncorrected threshold, one in the left superior

frontal gyrus (MNI: -15, 21, 57, Z = 2.98) and another in the left supplementary motor area (MNI: -14, 2, 65, Z = -2.06).

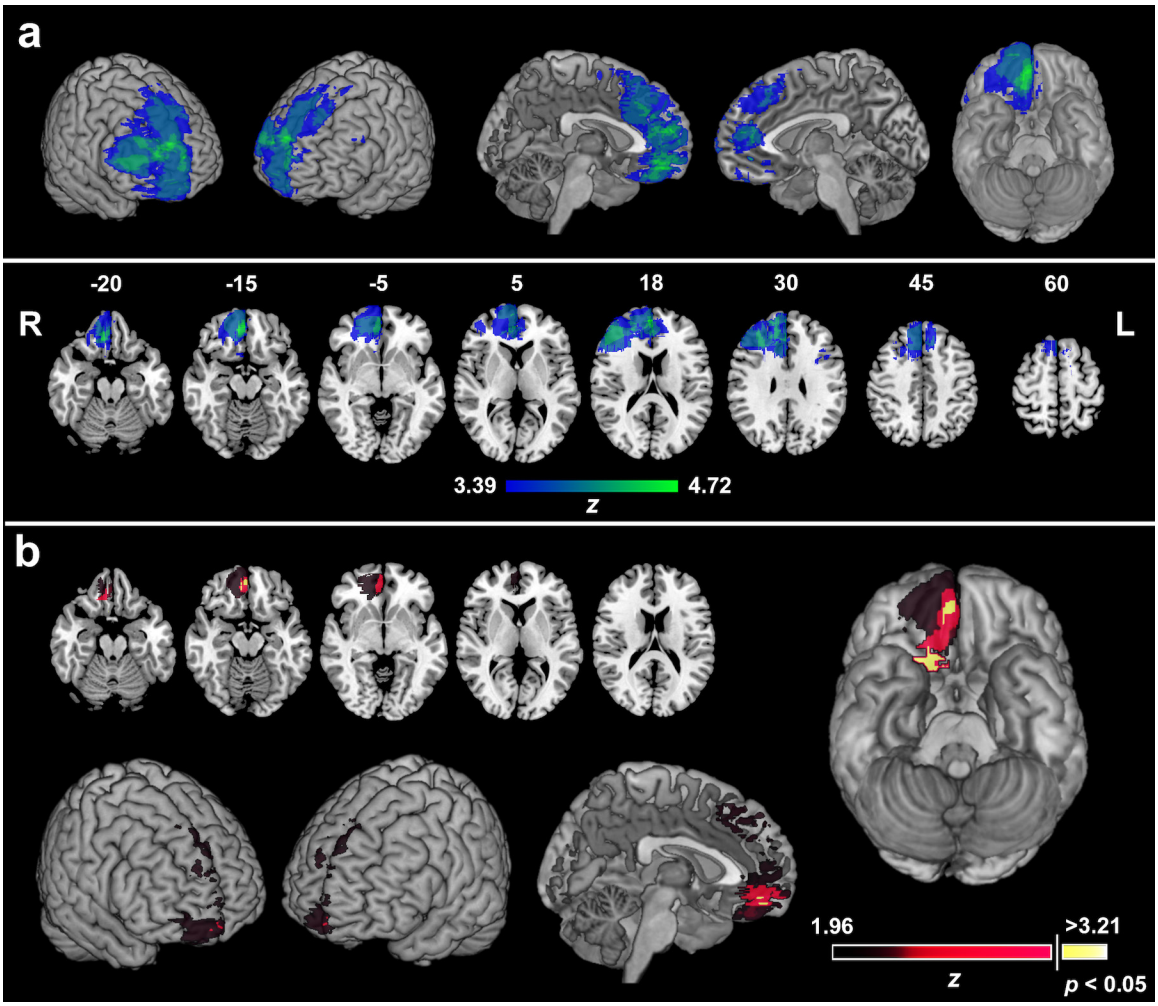

Figure 2.5. Voxel-based lesion symptom mapping (VLSM) analysis. **a**, Map showing the voxels where there was sufficient lesion overlap to detect an effect using VLSM methods, overlaid on the MNI brain in three-dimensional views (top), and in axial slices (bottom). Numbers above the axial slices correspond to z-coordinates in MNI space. The color scale indicates the maximum z-score detectable at a given voxel, indicating the power to detect effects above the permutation corrected criterion for statistical significance. R, Right L, Left. **b**, VLSM statistical map for diminished, or reversed, priming by reward-color associations overlaid on the MNI brain on representative axial slices (top), in three-dimensional and mid-sagittal view (bottom), and on ventral surface (right). The color scale indicates Brunner-Munzel Z scores. Statistical map is thresholded at $P < 0.05$, uncorrected. Voxels in yellow indicate where this effect was significant at $P < 0.05$, corrected with permutation tests.

Discussion

We examined the role of VMF in priming attention to stimulus features associated with different levels of reward during a visual search task. We observed that controls, and PFC patients with damage outside of VMF, showed greater priming by the color associated with higher overall reward compared to the color with lower overall reward, replicating previous work with similar tasks in healthy subjects (Hickey et al., 2010a; Kristjansson et al., 2010). Reward priming was significantly reduced in VMF patients compared to other groups. These results confirm our hypothesis, implicating VMF in guiding attention based on reward history.

Importantly, rewards in this experiment were incidental to the task itself, which simply required that subjects report the orientation of a target stimulus. This allowed us to test how attention is biased by reward independent of explicit task goals, shedding light on a potential mechanism underlying prior observations of impaired value-based learning and decision-making after VMF damage (Fellows, 2011; Zald & Andreotti, 2010). While directing attention to reward-predictive cues was not adaptive in this setting, this behavior is critical in the far more common situation when goals and rewards are aligned.

An inability to form an attentional set for stimulus features based on feedback could explain the performance deficits in particular learning tasks observed following VMF damage: Associative learning impairments have been observed after VMF, or orbitofrontal, damage in humans and non-human primates, but only under specific conditions (Butter, 1968; Hornak et al., 2004; B. Jones & Mishkin, 1972; J. L. Jones et al., 2012a; Noonan et al., 2010; Tsuchida et al., 2010; Walton et al., 2010, but see Rudebeck et al., 2013). Damage to this region does not affect learning about the reward value of stimuli in deterministic

settings (Dias et al., 1996a; Fellows & Farah, 2003), or learning to associate probabilistic reward to actions (Camille, Tsuchida, et al., 2011; Rudebeck, Behrens, et al., 2008). Orbitofrontal lesions in monkeys do not affect updating the value of primary rewards themselves, but rather the ability to associate this value to a paired stimulus (Rudebeck & Murray, 2011b). Thus, damage to this region appears to disrupt the formation of stimulus-reward associations based on ambiguous information, while leaving sensitivity to the rewards themselves intact.

In the current study, there was no measure of subjects' ability to learn stimulus-reward associations beyond the reward priming effect that was the primary dependent measure. Thus, we cannot definitively disambiguate whether VMF patients were impaired in allocating attention to reward primed cues, or in learning the reward associations of those cues. Indeed, these processes are linked under most conditions, with reward modulation of the attentional set fundamental to successful learning in dynamic or ambiguous situations. Consistent with this claim, the reward priming effect remained low in the VMF group over the course of the experiment, arguing that these patients did not direct attention to reward predictive cues even after extensive experience.

We believe that the current results provide new insights into the mechanisms underlying associative learning deficits following VMF damage. Within associative learning models, attention is generally thought to enhance learning about attended stimulus features (Le Pelley, 2010b). In this framework, attention is directed to features based on their predictive value, providing an additional layer of learning about the nature of the environment that adjusts the gain on prediction errors for individual stimulus features (Le Pelley, 2010a; Mackintosh, 1975; Pearce & Hall, 1980; Pearce & Mackintosh, 2010). We

suggest that failure to direct attention to reward-predictive visual features may explain deficits in learning stimulus-value associations after VMF damage. As a result, the signal-to-noise ratio on new information would be lower for these patients, impairing learning. This ability would be particularly critical in complex environments where options are defined by multiple features (Niv et al., 2015; Wilson & Niv, 2012).

This idea shares similarities with the hypothesis that orbitofrontal cortex is involved in 'model-based' learning – forming a cognitive map of the choice environment that facilitates decision-making (Daw & O'Doherty, 2013; Stalnaker, Cooch, & Schoenbaum, 2015; Wilson, Takahashi, Schoenbaum, & Niv, 2014). This theory argues that this region is involved in inferring the value of stimuli based on feedback history. Inferred, or model-based, values could set attentional priority for reward predictive features to filter information for future learning. In keeping with this theory, orbitofrontal lesions in rats reduce the sensitivity of dopaminergic neurons in the ventral tegmental area to prediction errors (Takahashi et al., 2011), which are considered a physiological correlate of the teaching signal described by animal learning theorists (Schultz et al., 1997).

Directing attention to reward predictive cues might also have effects on decision-making more generally. Attentional bias to reward associated stimuli is thought to reflect the activation of the behavioral approach system (Gray, 1991; Ikemoto & Panksepp, 1999), or a change in the incentive salience of previously neutral stimuli (Maunsell, 2004; Robinson & Berridge, 1993). Orienting to reward predictive stimuli might shift the balance in the competition between various options during deliberation. This sort of biased competition has been suggested as a mechanism by which PFC could influence selective

attention (Desimone & Duncan, 1995), and decision-making (Cisek, 2012; Cisek & Kalaska, 2010; Miller & Cohen, 2001).

While we anticipated that VMF damage would result in a reduction in priming by the high reward color, VMF damaged patients trended toward enhanced priming for the low reward color. While this effect was not statistically significant, it is possible that some of these patients overemphasized rare, incongruent, feedback where high rewards were paired with the (usually) low reward target color. This sort of maladaptive priming could result from an impaired representation of the variance of rewards linked to the two colors, in line with electrophysiological evidence that orbitofrontal neurons encode this information (O'Neill & Schultz, 2010; Schultz, O'Neill, Tobler, & Kobayashi, 2011). Testing the influence of incongruent rewards on attentional priming might give insight into this result, but there were not enough such trials in the current dataset to test this hypothesis reliably. This observation raises the possibility of multiple neural mechanisms for reward priming; further work will be needed to address this.

The current study raises questions about how VMF might influence visual attention based on feedback. One possibility is that VMF directly influences attention to reward associated stimuli through its connections with higher order sensory regions (Barbas et al., 2011; Carmichael & Price, 1995b). Magnetoencephalography data indicate that VMF and ventral visual regions communicate within a time frame that could allow VMF to directly influence selective attention processes underlying visual search (Bar et al., 2006; Luck, Woodman, & Vogel, 2000). Alternatively, VMF might influence sensory regions through a mediator region or a more complicated network. Recent evidence points to a role for the lateral intraparietal area (LIP) in representing the information value of cues for predicting

future rewards (Foley, Jangraw, Peck, & Gottlieb, 2014; Peck, Jangraw, Suzuki, Efem, & Gottlieb, 2009). This region might play a role in assigning attentional priority to stimulus attributes based on value associations encoded by VMF, as recently suggested by Hunt et al. (2014). The amygdala and pulvinar nucleus of the thalamus could also mediate the influence of rewards on attention, similar to their proposed role in mediating attention to emotional stimuli (Pessoa & Adolphs, 2010).

While our VLSM analysis showed that damage to right VMF was associated with reduced reward priming, the apparent lateralization of this effect is likely a consequence of the limited coverage of the left VMF in the current sample. There was also limited coverage of lateral orbitofrontal cortex, which is more directly connected with ventral visual areas (Price, 2007), possibly leading to false negatives in our analysis for that region. It is also worth noting that these lesions affect underlying white matter, which may influence brain regions distant from the site of injury. While white matter damage is represented in lesion overlap images, and tested by VLSM, we cannot fully distinguish the effects of white matter interruption on behavior from cortical damage based on these data alone. VLSM may also be biased towards the region of maximal overlap in a given sample, affecting the anatomical precision of structure-function claims (Kimberg et al., 2007; Mah, Husain, et al., 2014). However, this does not limit the inferences that can be drawn from the primary region-of-interest analysis. Further work using complementary methods (e.g. imaging, animal lesion models) will be important.

In summary, we showed that VMF plays a necessary role in reward priming of attention during a visual search task. These findings indicate that VMF facilitates the processing of cues that are predictive of rewards, even when not immediately task-

relevant. We suggest that VMF may bias processing of cues that are informative about future rewards in sensory-perceptual regions, in turn bootstrapping learning stimulus-reward relationships when there are multiple potentially reward-predictive cues, and influencing value-based decision-making.

Acknowledgements

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Chapter 3: Frontal contributions to multidimensional learning

Preface

In the last chapter, we showed that ventromedial frontal damage reduced attention to reward-predictive stimulus features that were incidental to the instructed task. Here, we turn to the question of how attention shapes reward learning. Selective attention is critical for adaptive learning when decision options have multiple competing dimensions that vary in predictive relevance (Kruschke, 2003; Mackintosh, 1975). Optimal performance in such situations often depends on ignoring irrelevant stimulus dimensions and attending to the dimension that is predictive of feedback.

In this next study, we tested how frontal lobe damage affects learning about multidimensional stimuli, where only one stimulus dimension has predictive value. Subjects with damage to the left lateral frontal lobe attributed rewards to salient, irrelevant stimulus dimensions, ignoring the relevant stimulus dimension. In contrast, subjects with ventromedial frontal damage were able to successfully filter out the salient, but irrelevant dimensions, yet failed to appropriately attribute rewards to the relevant stimulus dimension.

Necessary contributions of human frontal lobe sub-regions to reward learning in a dynamic, multidimensional environment

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Abstract

Real-world decisions are typically made between options that vary along multiple dimensions, requiring prioritization of the important dimensions to support optimal choice. Learning in this setting depends on attributing decision outcomes to the dimensions with predictive relevance rather than irrelevant, non-predictive dimensions. This attribution problem is computationally challenging, and likely requires an interplay between selective attention and reward learning. Both these processes have been separately linked to prefrontal cortex, but little is known about how they combine to support learning the reward value of multidimensional stimuli. Here, we examined the necessary contributions of frontal lobe sub-regions in attributing feedback to relevant and irrelevant dimensions on a trial-by-trial basis in humans. Patients with focal frontal lobe damage completed a demanding reward learning task where options varied on three dimensions, only one of which predicted reward. Participants with left lateral frontal lobe damage attributed rewards to irrelevant dimensions, rather than the relevant dimension. Damage to the ventromedial frontal lobe also impaired learning about the relevant dimension, but did not increase reward attribution to irrelevant dimensions. The results argue for distinct roles for these two regions in learning the value of multidimensional decision options under dynamic conditions, with the lateral frontal lobe required for selecting the relevant dimension to associate with reward, and ventromedial frontal lobe required to learn the reward association itself.

Introduction

Optimal decision-making requires attending to cues that reliably predict reward, often on a background of distracting or even misleading information. A trip down the grocery aisle reveals the daunting nature of this problem. For example, fruits vary on multiple dimensions (e.g. color, texture), each with their own features (e.g. red or green, soft or firm) that could guide choice. However, some dimensions are more relevant than others, or may be physically salient, but entirely irrelevant (e.g. the color of the packaging). How learning is optimized in such multidimensional settings has long been a challenging problem for normative computational models (Sutton & Barto, 1998), and animal learning theory (Pearce & Mackintosh, 2010), and is increasingly recognized as an important question in decision neuroscience (Niv et al., 2015).

Multidimensional learning requires attributing outcomes to features that are predictive of rewards, while ignoring non-predictive features. However, stimuli that have been spuriously correlated with outcomes, or are more salient than the predictive stimulus may be maladaptively credited with predictive value (Pavlov, 1927; Wilson & Niv, 2012). Attentional mechanisms aid learning in such settings by selecting between relevant and irrelevant features (Kruschke, 2003; Mackintosh, 1975; Rombouts, Bohte, Martinez-Trujillo, & Roelfsema, 2015).

Within the frontal lobes, lateral PFC has been implicated in selecting between relevant and irrelevant features of the environment for goal-directed behavior (Desimone & Duncan, 1995; Miller & Cohen, 2001). Lesions to this region in monkeys and humans disrupt attentional shifting between stimulus dimensions (Dias et al., 1996a; Milner, 1963), and attention to non-salient, but task-relevant, stimulus dimensions (Glascher et al., 2012;

Rossi, Bichot, Desimone, & Ungerleider, 2007; Tsuchida & Fellows, 2013). Lateral PFC lesions in humans or monkeys do not affect learning of stimulus-reward associations when cues are simple and unvarying (Dias et al., 1996a; Tsuchida et al., 2010). However, hemodynamic signal in lateral PFC correlates with attentional demands in a multidimensional learning environment (Niv et al., 2015). Whether this region is required for reward learning under these attentionally-demanding conditions is unknown.

In contrast, the ventromedial frontal lobe (VMF, here referring to both orbitofrontal (OFC) and ventromedial prefrontal cortex (vmPFC)) is necessary for optimal learning of dynamic stimulus-reward relationships. VMF damage impairs the ability of monkeys and humans to learn probabilistic and reversing stimulus reward associations for simple predictive cues (Butter, 1968; Fellows & Farah, 2003; Hornak et al., 2004; Tsuchida et al., 2010). Unlike lateral PFC, VMF damage does not affect attentional set shifting, or the ability to ignore salient, task-irrelevant stimulus dimensions (Dias et al., 1996a; Glascher et al., 2012; Milner, 1963; Tsuchida & Fellows, 2013). This region has thus not been considered as playing a role in attention.

However, recent work suggests that VMF may contribute to attentional selection during value-based learning and decision-making (Walton et al., 2015). VmPFC value signals measured with fMRI are sensitive to the behavioral relevance of option dimensions during choice (Hunt et al., 2014; Lim et al., 2013), and VMF is critical for attentional priming of rewarded stimulus features (Vaidya & Fellows, 2015). The interaction of vmPFC and lateral PFC is also correlated with selection of relevant stimulus features during decision-making (Chau et al., 2014; Hare, Malmaud, & Rangel, 2011). Together, these

studies raise questions about the necessary contributions of these regions during value-based choice between complex stimuli.

The aim of this study was to test the necessary contributions of frontal lobe sub-regions to optimal learning in a multidimensional task environment. Patients with frontal lobe damage completed a probabilistic reversal learning task where stimulus options were defined by three dimensions, only one of which predicted feedback. We focused on trial-by-trial behavior, testing the effects of frontal lobe damage on feedback attribution. Left lateral frontal damage increased attribution of rewards to irrelevant dimensions, and decreased attribution to the relevant dimension. VMF damage also affected learning in the relevant dimension, but not reward attribution to irrelevant dimensions. These results demonstrate potentially distinct roles for these regions during learning in a complex environment.

Materials and Methods

Subjects

Forty-five patients with focal lesions involving the frontal lobes were recruited for this study, 36 from the Cognitive Neuroscience Research Registry at McGill University, and 9 from the Center for Cognitive Neuroscience at the University of Pennsylvania (Fellows et al., 2008). They were eligible if they had a fixed lesion primarily affecting the frontal lobes. Patients were categorized into groups *a priori* following standard anatomical boundaries (Stuss et al., 2005), based on the location of their damage, assessed on their most recent MR or CT imaging, by a neurologist blind to task performance. Patients with lesions primarily affecting VMF were identified first, as the primary region-of-interest. The remaining patients were then subdivided further into dorsomedial frontal (DMF), left lateral frontal (LLF) and right lateral frontal (RLF) groups. Lesions were manually

registered to a common brain space (MNI brain) to allow overlap images to be generated. The overlap images for the four anatomically defined groups are shown in Figure 3.1.

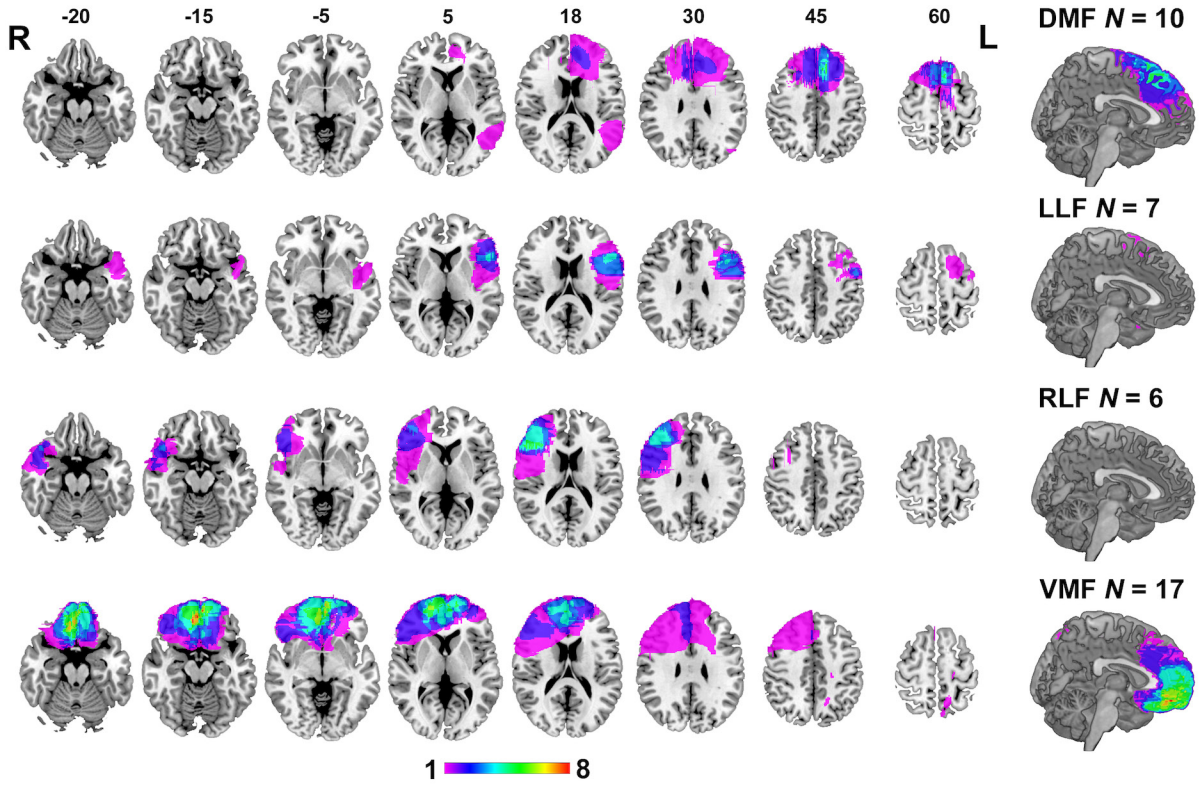

Figure 3.1. Representative axial slices and sagittal view of overlap of lesion tracings on the MNI brain. Rows show overlap in the dorsomedial frontal (DMF), left lateral frontal (LLF), right lateral frontal (RLF) and ventromedial frontal (VMF) groups. Numbers above slices indicate z coordinates of axial section in MNI space. Colors indicate number of subjects with overlapping lesions, as indicated by the color bar. L, left; R, right.

One VMF patient found the task too difficult and asked to stop the experiment after the first block. Three other patients were excluded from further analysis because their choices indicated that they were following idiosyncratic rules unrelated to the task instructions or feedback: One patient with DMF damage appeared to be deliberately avoiding previously rewarded features, one patient with VMF damage chose the green stimulus on nearly every trial, without any regard to feedback or any other task dimensions, and one DMF patient simply chose stimuli in one color throughout the first two

and half blocks of the experiment, alternating the color between blocks. A fifth patient was excluded from analysis when it was found that the boundaries of her lesion could not be accurately established. The final sample included 40 patients with frontal lobe damage, 19 males and 21 females.

Damage to DMF was caused by tumor resection in nine cases and ischemic stroke in one case. Damage to LLF was caused by ischemic stroke in five cases, aneurysm in one case and tumor resection in one case. Damage to RLF was caused by tumor resection in four cases and ischemic stroke in two cases. Damage to VMF was caused by tumor resection in nine cases, hemorrhagic stroke in four cases, aneurysm in three cases and ischemic stroke in one case. Patients were tested in the chronic phase. The median time since brain injury (defined as the onset of symptoms for stroke or aneurysm rupture, and the date of surgery for tumor resection) was 8.25 years (range, 3.5 months to 48.1 years). Nineteen patients were taking one or more psychoactive medications, most commonly an anticonvulsant or anti-depressant. There was a marginally significant difference in the frequency of psychoactive medication usage between groups (Chi squared test of independence: χ^2 = 7.82 (3), p = 0.05), with more patients in the DMF group taking such medications (80%) compared to other patient groups (VMF (47%), RLF (33%) and LLF (14%)).

Age- and education-matched healthy control subjects (N = 21; 8 men and 13 women) were recruited through local advertisement in Montreal. They were free of neurological or psychiatric disease and were not taking any psychoactive medication. They were excluded if they scored 26 or less on the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005). Mean performance on this test was 28.3, SD = 1.5. All subjects provided written informed consent in accordance with the Declaration of Helsinki and were compensated

with a nominal fee for their time. The study protocol was approved by the institutional review boards of both participating centers.

Neuropsychological screening

All patients completed neuropsychological screening to test general cognitive functioning. Patients at both institutions underwent screening for hemispatial neglect using the Posner cueing task (Posner, 1980), and a circle cancellation task (Marsh & Hillis, 2008). These patients also completed tests of working memory (backwards digit span; Lezak, Howieson, Bigler, and Tranel (2012)), and semantic and phonemic verbal fluency (Fluency-F, Animals) (Benton, Hamsher, & Sivan, 1989). Patients recruited from the Cognitive Neuroscience Research Registry at McGill University also completed a test of visual memory for faces without explicit instructions (incidental memory) (Bower & Karlin, 1974), and a test of the ability to understand and follow 1, 2 and 3-step verbal instructions (sentence comprehension, similar to the Token Test (Derenzi & Vignolo, 1962)).

Apparatus

The experimental task was programmed using E-Prime 1.2 (Psychology Software Tools, Inc., Pittsburgh, PA, USA). Twenty-nine patients and all 21 controls were tested at the Montreal Neurological Institute. They saw stimuli presented on a 19-inch monitor (Dell Inc., Round Rock, TX, USA) and responded using the left- and rightmost keys on a serial response box (Psychology Software Tools, Inc., Pittsburgh, PA, USA). Eleven patients tested at the University of Pennsylvania, and in home visits in the greater Philadelphia and Montreal areas, performed the experiment on a 13.5 inch laptop (Fujitsu Ltd., Tokyo, Japan) and used the left and right arrow keys of the laptop keyboard for their responses.

Two patients with VMF damage used the index and middle fingers of their right hands due to weakness in the left hand. All other subjects responded bimanually.

Procedure

Subjects completed a multidimensional, probabilistic reversal learning task. In this task, subjects chose between two compound stimuli, described in the instructions as 'cards,' that were defined by a shape (a backwards or forwards facing 'C') and color (blue or green) and appeared on the left and right sides of the screen. Subjects chose between these two options on each trial by pressing the corresponding right or left key. Critically, only the shape inside the card was relevant to whether or not subjects would be rewarded. One shape was associated with a 75% chance of reward, while the other shape was associated with a 25% chance of reward. Once subjects had chosen the probabilistically more rewarding shape in 10 out of the previous 12 consecutive trials (i.e. once more than would be achieved by simply using a win-stay, no win-shift strategy, on average), the reward probabilities for the two shapes would reverse. The color and side of the stimulus had no predictive value for determining feedback. Mirror shapes were chosen as the relevant stimulus to place greater demands on selective attention. Mirror shapes are relatively difficult to discriminate (Cooper, 1975; Corballis & Mclaren, 1984), and thus less salient than the features of the color and side dimensions, a notion supported by associative learning work in monkeys (Baxter & Gaffan, 2007).

At the beginning of the experiment, subjects were given the following instructions "You are going to play a card game. You will see two cards on either side of the screen. Your job is to choose one of the cards. You will either receive points or get nothing after making a choice. Only the shape inside the card is relevant to whether you will be rewarded. The

color is irrelevant. One shape is better than the other, however no shape is always rewarding. So, you should try to STICK WITH one shape. Be careful, because the better shape may also change. The points you receive will be converted to money at the end of the experiment." These instructions were deliberately very similar to previous work from our group using a probabilistic reversal learning task (Camille, Tsuchida, et al., 2011; Tsuchida et al., 2010), with additional information added regarding the relevant and irrelevant stimulus dimensions unique to this experiment. After reading these instructions, subjects were asked to explain what they were supposed to do to the experimenter to check their understanding.

On each trial, subjects would first see a central fixation point for 500 ms, followed by presentation of the two options (i.e. cards) on either side of the screen for 600 ms. These stimuli were subsequently replaced by a mask (a black 'O' card) for 500 ms. Subjects were allowed to respond at any point in this 1100 ms window, from stimulus presentation to the end of the mask presentation. Following the mask, subjects were shown a feedback screen that lasted 800 ms. Subjects were explicitly instructed that they could still respond after the cards had disappeared, until they saw feedback.

On the feedback screen in each trial, subjects saw a running total of the number of points they had earned thus far in the center of the screen. The option selected on that trial was presented above the total. On trials where subjects won points, they would hear a high pitched 'ding' sound and see the text 'Win!' written in yellow below the total. On trials where no points were won, subjects would not hear any sound or see any other text. If the subject did not respond, or did not respond in time, subjects simply saw the total number of points with the text 'Respond faster' written above.

Subjects completed four blocks of this task, with 200 trials in each block for a combined 800 trials total. Two control subjects, two VMF patients, one DMF patient and one RLF patient, chose stimuli in only one color in nearly all trials of the first block, without regard to the feedback. These subjects were re-instructed after the end of the block, and responded to feedback in subsequent blocks. The data from this first block were excluded from analysis in these subjects.

Voxel-based lesion symptom mapping

In a secondary analysis, we used voxel-based lesion symptom mapping (VLSM) to test where brain damage was associated with reduced win-stay behavior for the relevant shape dimension, and increased win-stay behavior for irrelevant color and side dimensions, as measured by parameters from a multiple logistic regression analysis. Given that VLSM analysis removes matching for demographic factors that may be related to performance, we tested if these three variables were related to age or education in control subjects using multiple linear regression, and applied corrections to parameters where necessary (see statistical analysis section). These parameters were then used in the VLSM analysis using Non-Parametric Mapping (NPM, version June 6, 2013) software (freely available at www.mccauslandcenter.sc.edu/mricro/npm/). This analysis compared patients with damage at each voxel with the rest of the patient group using non-parametric Brunner-Munzel (BM) tests (Brunner & Munzel, 2000). Only voxels where there were three or more patients with lesion damage were included. Due to the large number of multiple comparisons involved in this test, a null distribution of BM *Z*-scores was calculated from the same dataset using permutation tests (3000 permutations) to find an appropriate threshold for the adjusted alpha rate (Nichols & Holmes, 2002). Permutation tests provide

an assumption free means for controlling the rate of false positives after multiple comparisons, with more statistical power than overly conservative methods like the Bonferroni correction (Kimberg et al., 2007). Images of the results of this analysis were created using the software MRICron.

Statistical analysis

Demographic measures for patient groups (age, years of education, and Beck Depression Inventory-II) and performance on neuropsychological screening tests were compared to controls using uncorrected between-subjects t-tests. AMNART estimated IQ and lesion volume in patient groups were compared with uncorrected, non-parametric Mann-Whitney U-tests, as these values were not normally distributed.

Group differences in performance on neuropsychological screening tests were assessed using one-way ANOVAs, or non-parametric Kruskal-Wallis tests (for circle cancellation, sentence comprehension). Where there were any significant, or trending, effects of group status, *post-hoc* uncorrected between-subjects t-tests, or Mann-Whitney U-tests were used to assess these differences.

To assess basic performance data, a chi-squared test of independence was used to examine if the overall frequency of trials (misses and choices of the high or low reward probability shapes) differed between groups. Effects of group status on the frequency of choices of the more rewarding shape (excluding missed responses), and the frequency of reversals per block, were tested with a Kruskal-Wallis test. The effect of experimental block on the frequency with which subjects chose the high reward probability shape was tested using a mixed-measures ANOVA. An arcsine transformation was used to ensure that these frequency values were normally distributed. Post reversal accuracy was tested using a

mixed-measures ANOVA to examine the effects of group status, and post-reversal trial number on the frequency with which subjects chose the high reward probability shape. Subjects who achieved fewer than three reversals were omitted from this analysis (3 controls, 2 DMF, 1 LLF, 1 RLF and 1 VMF)). Again, an arcsine transformation was used to ensure that these frequency values were normally distributed.

Group differences in overall reaction times were tested using a one-way ANOVA. Effects of the trial-by-trial repetition of the color and side of the previously rewarded shape were tested for using a mixed-measures ANOVA, with the color and side repetition of the chosen shape as within-subjects factors and group status as a between-subjects factor.

Generalized estimating equations (GEEs) as implemented in SAS (version 9.4, SAS Institute Inc., Cary, NC, USA) were used to examine trial-by-trial behavior. This analysis is very similar to a mixed model regression, but is more robust to misspecification of the variance structure. This method allowed us to take full advantage of the relatively large number of observations per subject in this experiment while comparing average differences in group performance. To test the effects of group status on staying with the rewarded features in each stimulus dimension, we modeled the probability that subjects chose the left option in trials immediately following a reward, as a function of whether the shape or color chosen in the last trial were on the left, and whether subjects chose the left side in the last trial. We first estimated parameters for this model in the control group separately to examine learning in healthy subjects in this task. Next, we analyzed the full data set, including main effects of group status and interactions between each of these variables and group status, referenced to the parameter estimates for control subjects. An

identical analysis was used to test trial-by-trial effects for switching away from features paired with negative feedback (i.e. absence of rewards) in the previous trial.

Effects of positive and negative feedback history were also analyzed using a GEE model. We calculated the frequency with which features in the left and right options in a given trial were associated with positive (rewards) and negative (no reward) feedback in the last four trials. We then estimated how the difference in frequency of positive and negative feedback between the features in the left and right options was related to the probability of choosing the left or right option. This analysis tested how the relative value within each dimension, as learned in recent trials, was weighted in subjects' choices. As in the trial-by-trial analysis, we first estimated these parameters in the control group alone before testing the interaction between group status and positive and negative feedback history for each stimulus dimension.

We also explored whether the information value within each dimension affected trial-by-trial attribution of feedback to the same dimension, and other stimulus dimensions. We operationalized information value here as the absolute value of the difference in reward frequency for features within each stimulus dimension, in the last four trials (similar to choice history). Given that subjects were influenced most by the association of features with rewards, rather than the absence of reward, and the effects of group status were principally related to changes in reward attribution, we focused on information value about positive feedback, not negative feedback. In three separate GEE models, we estimated the probability that subjects would stick with a previously rewarded shape, color or side, given the information value within each dimension. As in the previous GEE analyses, we first tested these effects in healthy control subjects before analyzing the

effects of group status. Finally, to acquire individual estimates of win-stay behavior for each subject for use in VLSM analysis, we carried out a multiple logistic regression analyses on subject level data. Win-stay behavior was modeled the same way as in the GEE analysis at the group level (i.e. estimating how the probability of choosing the left or right option depended on whether these options contained features previously rewarded in the last trial). Patient parameters for win-stay behavior in the side and shape dimension were adjusted for age and education level, as these parameters was significantly predicted by these factors in the control group in multiple linear regression analyses. Education level in these analyses was categorized as high school or less, some college to a college degree, and some graduate education to a graduate degree. To adjust for these effects, we calculated predicted parameters for win-stay behavior in these dimensions for each patient based on the relationship between these parameters and education level and age in the healthy control group. The residuals between these predicted parameters and parameters estimated from individual patients' behavior were then calculated and used in the VLSM analysis.

Results

Demographic information and lesion volumes are provided in Table 3.1, and neuropsychological screening results in Table 3.2. Both VMF and DMF groups scored higher than controls on the Beck Depression Inventory-II, but lesion groups did not differ from each other on this measure. VMF damaged patients also scored lower than controls and DMF damaged patients on AMNART estimated IQ (though this measure was not available for all subjects). RLF patients scored higher than other patient groups on a test of verbal fluency. There were no group differences in performance on tests of language

comprehension, memory, executive function and spatial attention, nor in lesion volume (*P*'s > 0.05, uncorrected between-subjects t-tests, Mann-Whitney U-tests).

Table 3.1. Demographic information for controls and prefrontal patients. Values represent means with standard deviations in parentheses, except for lesion volume where the median and range are provided.

Group	Age (years)	Sex (M/F)	Education (years)	BDI-II	AMNART IQ [a]	Lesion Volume (cc)	Handedness (right/left/ both)
CTL (N=21)	59.7 (10.9)	8/13	15.1 (3.4)	4.4 (4.3)	119 (4)	-	18/2/1
DMF (N = 10)	57.8 (5.1)	5/5	15.0 (4.3)	8.9 (6.2)*	120 (5)	14 (3-83)	8/2/0
LLF (N = 7)	63.3 (10.8)	4/3	14.7 (3.0)	4.7 (3.3)	117 (10)	17 (5-47)	7/0/0
RLF (N=6)	57.5 (6.2)	3/3	15.3 (3.6)	8.5 (8.1)	120 (6)	24 (22-96)	5/1/0
VMF (N = 17)	60.9 (10.2)	7/10	14.5 (3.2)	9.8 (6.9)*	110 (7)^	20 (7-192)	15/1/1

[a] Not all subjects were able to complete the AMNART. * $P < 0.05$, two-tailed *t*-test against control scores, uncorrected. ^ $P < 0.05$, two-tailed Mann-Whitney U test against control and DMF scores, uncorrected.

Table 3.2. Performance on neuropsychological screening tests for controls and prefrontal patients. Values represent means with standard deviations in parentheses, except for sentence comprehension where the median and range are given instead.

Group	Posner Cueing (Uncued-Cued) Left/Right (ms)	Circle cancellation % missed (Left/ Right)	Circle cancellation % false alarms	Fluency - animals	Fluency - F	Backwards Digit Span	Incidental memory P(Correct)^	Sentence comprehension P(Correct)^
CTL (N=21)	81.2 (37.8) 54.2 (34.5)	- -	-	-	-	-	-	-
DMF (N = 10)	77.6 (59.5) 72.8 (49.9)	0.4 (0.8) 1.1 (2.4)	0.06 (0.2)	19.1 (8.6)	8.9 (5.8)*	2.3 (1.3)	0.78 (0.13)	0.99 (0.88-1.00)
LLF (N = 7)	65.9 (31.4) 86.8 (32.0)	0.5 (1.0) 0.7 (1.2)	0.71 (1.9)	17.8 (7.9) [a]	8.2 (3.7)* [a]	2.7 (1.2)	0.81 (0.12)	0.95 (0.83-1.00)
RLF (N=6)	50.6 (56.3) 32.8 (39.0)	1.7 (2.9) 1.0 (2.0)	0.31 (0.5)	22.0 (2.7)	14.5 (3.6)	2.8 (1.2)	0.82 (0.11)	0.95 (0.77-1.00)
VMF (N = 17)	72.8 (37.5) 57.2 (37.5)	1.6 (2.0) [a] 1.9 (2.7)	0.08 (0.2)	17.7 (3.5) [b]	10.2 (4.4)* [b]	3.2 (1.3)	0.85 (0.11)	0.95 (0.77-1.00)

^Montreal patients only, [a] Data missing from one patient. [b] Data missing from two patients.
* $P \leq 0.05$, against RLF two-tailed *t*-test, uncorrected.

Subjects performed the probabilistic reversal learning task shown in Figure 3.2. This task was designed to test how subjects attributed feedback to stimulus features at the trial-by-trial level. In each trial, subjects chose between two options that were defined by three dimensions: a relatively non-salient shape (forwards or backwards 'C'), a color (green or blue) and the side of presentation (left or right). Note that side of presentation refers here to both the position of the stimulus on the screen and the response required to select it (i.e. left or right button press). However, only features within one dimension (shape) were predictive of whether or not an option was rewarding (75% or 25% chance of reward). Subjects were informed that only the shape was relevant, and that rewards were probabilistic before beginning the task. Once subjects met a criterion indicating that they had learned the shape-reward association, this relationship was reversed. This criterion condition ensured that the frequency of reversals was matched to subjects' performance level. Reversals in this task were not themselves of primary interest, but were included to ensure that the task remained difficult for all subjects and to prevent the adoption of a simple rule-based response strategy.

The task consisted of four blocks, each lasting 200 trials. In each trial, the two options were comprised of combinations of shape, color and side features such that all features were represented in every trial, and all combinations of option features were equally represented in each block. Thus, from trial to trial, the features defining each option could either remain the same or differ along multiple dimensions. Optimal performance in this task required subjects to continuously track the changing values associated with these shapes, while filtering out information from other stimulus dimensions that was not

predictive of rewards. Thus, this task taxed subjects' ability to direct selective attention for the optimization of reward learning in a dynamic, challenging environment.

Studies of visual search have shown that similar trial-by-trial manipulations prime attention to task-irrelevant features of previously selected targets (i.e. priming of pop-out; Kristjansson and Campana (2010); Maljkovic and Nakayama (1994)), and that this priming effect is modulated by feature-reward associations (Hickey et al., 2010b; Kristjansson et al., 2010). We also have recently shown that attentional priming for reward associated visual features is affected by VMF damage (Vaidya & Fellows, 2015). Here, we asked if such trial-by-trial attentional effects relate to the flexible reward learning deficits previously observed after VMF damage (Tsuchida et al., 2010). Stimuli were presented more briefly than is typical for reward learning tasks, and the predictive stimulus feature was less salient than non-predictive ('distracting') task features in order to place particular demands on the relatively rapid selective attention processes that were of interest in the present study (Hickey et al., 2010a; Sigurdardottir, Kristjansson, & Driver, 2008).

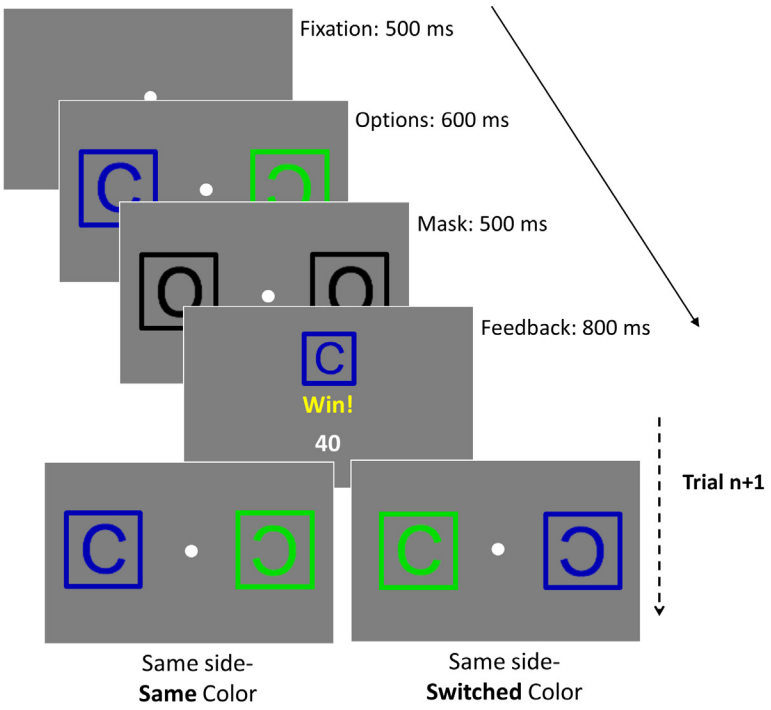

Figure 3.2. Task design. In each trial, subjects were shown a fixation cross for 500 ms, followed by two 'card' options on either side of the screen for 600 ms. These cards were then replaced by a mask for 500 ms. Subjects could respond at any point from the onset of the option slide to the termination of the mask slide. After a choice was made, subjects received feedback, a win (40 points) or no win (0 points), that was probabilistically dependent on the shape (forwards or backwards 'C') inside of the card. In the next trial, the color and side of these shapes would randomly stay the same or switch

Overall task performance

We first examined overall task performance, comparing the frequency of choices of the high- and low-reward probability shapes, as well as missed responses (i.e. failure to respond by the deadline) between groups across the whole task. There was a significant difference in the proportion of these responses between groups (Chi-squared test of independence: $\chi^2 = 295.39$ (8), $P < 0.001$), with the frontal groups missing more responses compared to healthy controls (Table 3.3). After excluding missed responses, there was no difference in the proportion of choices of the high vs. low reward shape between groups (Kruskal-Wallis test: H_4=3.67, $P = 0.4$; Figure 3.3A). Given the challenging nature of this task (multiple reversals, probabilistic reward, multiple stimulus dimensions), we expected

that overall performance would be far from optimal. Nonetheless, a majority of subjects in each group chose the high reward shape more often than expected by chance overall, though the proportion of the LLF group meeting this criterion was lower than in controls and other patient groups (Percentage of subjects above chance: Controls, 76.2%; DMF, 70.0%; LLF: 57.1%; RLF, 83.3%; VMF, 75.5%).

Table 3.3. Overall task performance. Values represent mean with standard deviation in parentheses.

Group	Choice high probability shape (%)	Choice low probability shape(%)	Missed (%)
CTL (N=21)	55.2 (7.8)	40.1 (7.8)	4.7 (2.6)
DMF (N = 10)	51.2 (9.5)	40.8 (7.2)	7.9 (5.8)
LLF (N = 7)	49.8 (4.7)	46.4 (3.1)	3.7 (2.4)
RLF (N=6)	50.0 (6.9)	43.6 (5.9)	6.4 (6.4)
VMF (N = 17)	51.2 (8.3)	40.9 (5.9)	7.8 (6.3)

We next tested if subjects' performance improved over the course of the experiment (Figure 3.3B), by comparing the frequency with which subjects chose the high reward shape across blocks. The first block of the experiment was dropped from analysis in some subjects (see methods). In these cases, the second block was considered the start of the experiment and only three blocks were considered in the analysis. For the majority of subjects, the third and fourth blocks were collapsed in this analysis. All groups showed evidence of learning, in that performance improved over the course of the experiment (Mixed-measures ANOVA: $F_{2,112} = 8.53$, $P = 0.0004$). There was no significant effect of group status ($F_{4,56} = 0.94$, $P = 0.4$), nor interaction between block and group ($F_{8,56} = 1.15$,

P = 0.3), in the frequency with which subjects chose the high reward shape. Thus, patient groups and controls generally improved as the task wore on.

We also examined the number of reversals per block to assess how often each group encountered reversals, and to test if these groups differed in the frequency with which they met the necessary learning criterion (Figure 3.3C). All subjects met the learning criterion for at least one reversal over the course of the experiment. There was wide variance in the number of reversals subjects experienced and a trend toward a difference between groups (Kruskal-Wallis test: H_4=7.96, P = 0.09), with frontal groups, particularly LLF damaged subjects, meeting the learning criterion less often than controls.

Flexible learning requires rapid adaptation to changing reward associations. Prior work has shown that VMF damage leads to prominent learning deficits under such conditions (Dias et al., 1996a; Fellows & Farah, 2003; Walton et al., 2010). In the current task, subjects struggled to consistently choose the high reward shape, potentially suggesting a near random pattern of responding. We examined post-reversal behavior to test if subjects met learning criteria by chance performance, or through deliberate selection of the high reward shape. We test for group difference in the selection of the high reward shape in trials immediately following reversals in subjects who achieved at least three reversals over the course of the experiment (Figure 3D). Overall, most subjects chose the shape (newly) associated with a high probability of reward at well below chance rate in the first trial after a reversal, consistent with a deliberate selection of the previously rewarded shape, and then increasingly more often in subsequent trials (Mixed-measures ANOVA: $F_{11,539}$ = 8.33 P < 0.0001). While the VMF group was numerically similar to controls, there was a modest trend toward an interaction between group and trial number ($F_{44,539}$ = 1.26 P

= 0.1), driven by the near chance performance of LLF damaged patients immediately following the reversal, in contrast to controls and the other patient groups. There was no significant main effect of group ($F_{4,49}$ = 1.29 P = 0.3) on this measure.

To summarize, these coarse, overall measures of task performance revealed that all groups struggled to consistently choose the most rewarding shape, a result that is perhaps unsurprising giving the challenging nature of this task. In spite of these difficulties, most subjects improved over the course of the experiment and met the learning criterion for reversals. The LLF group performed numerically worse than controls and other patient groups in all measures of overall task performance related to choosing the high reward shape, though no significant effects of group status were found in these measures.

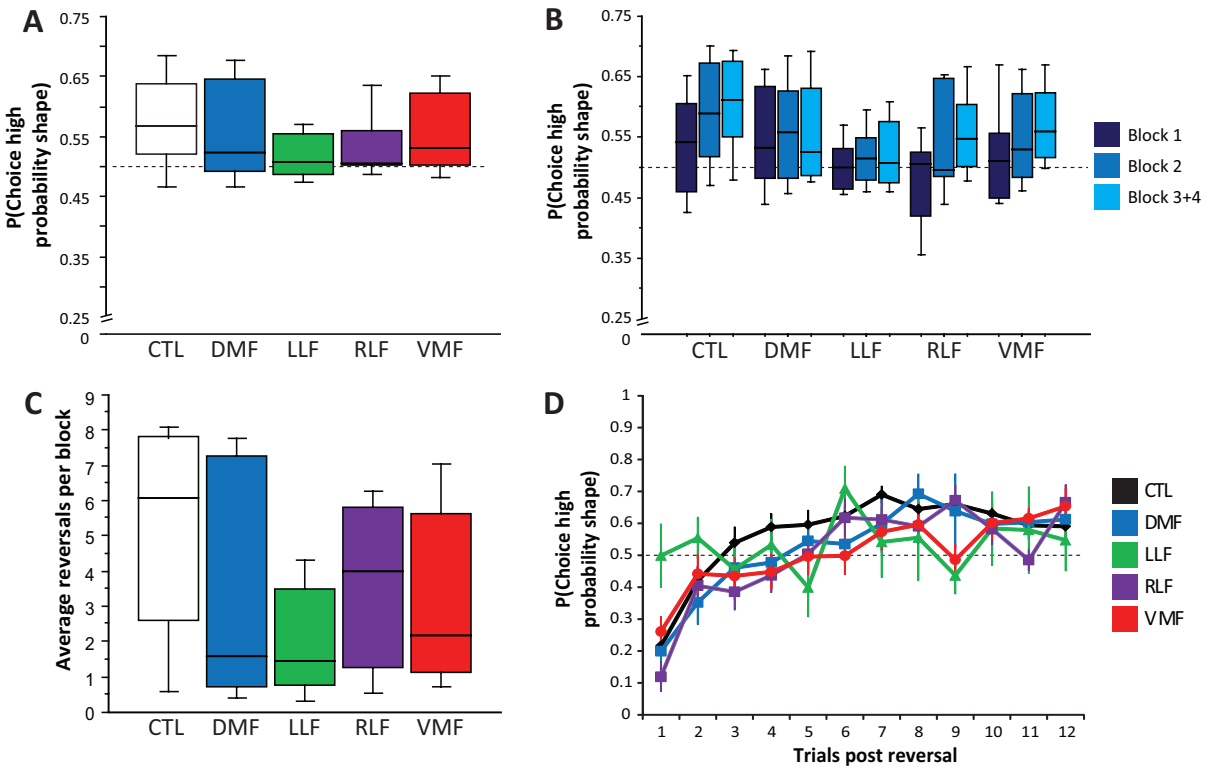

Figure 3.3. Measures of overall task performance. **A.** Overall probability of choosing shape with a high probability of reward. **B.** Probability of choosing shape with a high probability of reward over task blocks. **C.** Average number of reversals per block (i.e. frequency that

subjects met the learning criterion). **D.** Probability of choosing shape with a high probability of reward in trials immediately following a reversal. Dashed line indicates chance level performance. Box plots show the 10th, 25th, 50th, 75th and 90th percentiles of data. Error bars indicate SEM.

Trial-by-trial behavior

We were primarily interested in whether damage to specific frontal sub-regions affected the attribution of feedback to relevant and irrelevant stimulus features on a trial-by-trial basis. We expected that variability in the ability to maximize reward by choosing the better shape was likely related to differences in subjects' ability to selectively attend to this stimulus dimension, and perhaps to prioritize features within this dimension based on on trial-by-trial feedback. To assess this prediction, we used generalized estimating equations (GEEs) to test how feedback in the immediately previous trial (n-1) influenced subjects' choices on the current trial (trial n). This analysis maximized our sensitivity to detect effects at the level of trial-by-trial behavior, taking full advantage of the relatively large number of unique observations per subject, and the structure of the task itself, with random changes in the features composing each decision option from trial to trial. The GEE analysis estimated the probability that subjects would choose the left or right option, given the shape, color and side that subjects had chosen in the last trial (i.e. whether or not the previously chosen shape or color appeared in the left or right option, and whether subjects chose the left or right option in the last trial). For each parameter, we report an odds ratio and 95% confidence interval (CI) representing how each factor affected the probability of choosing the left or right option from trial to trial on a logarithmic scale.

We first tested how the association of relevant and irrelevant features with rewarding feedback (i.e. 'wins') affected the trial-by-trial behavior of healthy control subjects. Control subjects were significantly more likely to choose a shape (OR = 16.13, CI:

6.77-38.47, $P < 0.0001$), or color (OR =2.18, CI: 1.52-3.12, $P < 0.0001$) that had been rewarded in the previous trial, but not the side that had been rewarded (OR = 1.08, CI: 0.66-1.76, $P = 0.8$). We next examined the influence of lack of reward feedback (i.e. 'no win') on controls' trial-by-trial behavior. Absence of reward did not affect the probability that controls would repeat a choice of a previously chosen shape (OR = 1.01, CI: 0.65-1.58, $P = 0.9$), or color (OR = 0.94, CI: 0.81-1.10, $P = 0.5$) on the current trial, but did significantly decrease the likelihood of choosing the same side (OR = 0.50, CI: 0.33-0.75, $P = 0.0009$). Thus, while controls were strongly inclined to choose the shape that had been rewarded on the previous trial, they also frequently chose previously rewarded colors, despite the fact that these features were not consistently associated with reward feedback across trials (i.e. this dimension had no overall predictive value). Healthy controls also tended to avoid picking a previously unrewarded side, though this dimension was also, in fact, irrelevant (non-predictive). Thus, healthy control subjects' choices were influenced by feedback associated with relevant, predictive features, as well as irrelevant features with no predictive value.

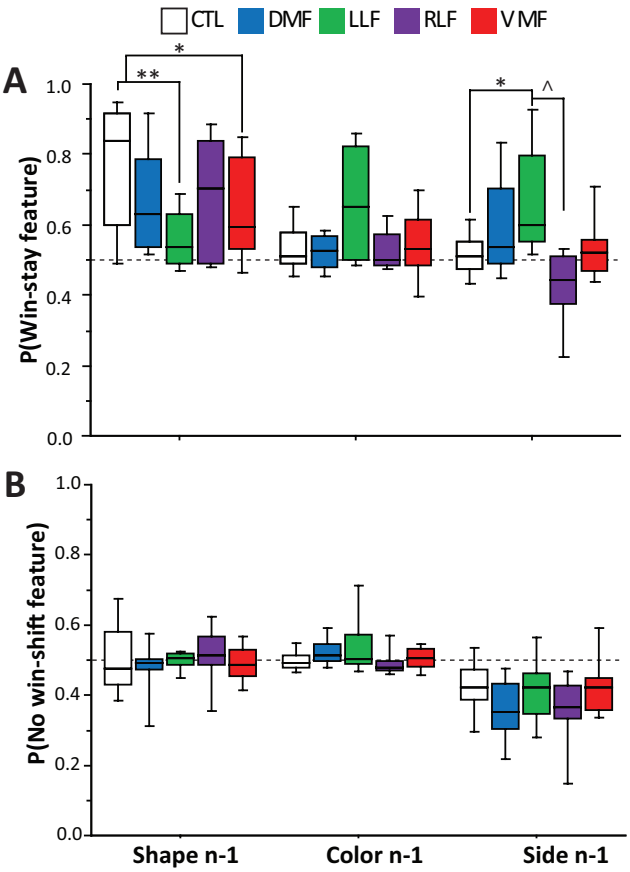

Figure 3.4. Analysis of trial-by-trial performance. **A.** Probability of staying with a feature after a rewarded choice. **B.** Probability of shifting away from a feature after an unrewarded choice. Dashed line indicates chance level responding. Box plots show the 10th, 25th, 50th, 75th and 90th percentiles of data. *$P < 0.05$, **$P < 0.0001$, generalized estimating equation coefficients, referenced to controls. ^$P < 0.05$, Bonferroni corrected t-test.

We next tested interactions between group status to examine the effects of regional frontal lobe damage. These interactions capture the relative influence of feedback on the previous trial on the likelihood of choosing the same feature again in the current trial in each patient group compared to the control group. This analysis allowed us to compare how frontal groups were influenced by the trial-by-trial association of positive and negative feedback with stimulus features. All odds ratios for group effects are reported with reference to the control group.

We first tested if frontal groups differed from controls in staying with previously rewarded shapes (i.e. win-stay behavior), and if these subjects were more likely to choose previously rewarded irrelevant features (color or side) (Figure 3.4A). The full results of this GEE can be found in Table 3.4. VMF and LLF damaged groups were significantly less likely than controls to select a previously rewarded shape. A similar trend was seen in the DMF damaged group. The LLF group was also significantly more likely than controls to choose the previously rewarded side. The RLF group showed a modest trend in the opposite direction (i.e. less likely to choose a previously rewarded side), as well as a modest, but significant, tendency to choose the left side more often overall. No significant differences were observed between patient groups and controls in the probability of choosing a previously rewarded color, although there was large variance in this effect within the LLF group. Post-hoc tests between frontal lobe damaged groups revealed a significant difference between RLF and LLF groups in their likelihood to choose a previously rewarded side ($P = 0.04$, Bonferroni-corrected t-test), and no other significant differences.

Table 3.4. Odds ratios (OR), 95% confidence intervals (CIs) and respective *P* values for trial-by-trial win-stay behavior within all three dimensions.

	Effect	**OR (95% CI)**	***P* value**
Main Effects	Intercept	OR = 0.14 (0.08-0.26)	<0.0001
	DMF	OR = 1.29 (0.58-2.85)	0.5
	LLF	OR = 0.79 (0.38-1.62)	0.5
	RLF	OR = 2.70 (1.13-6.45)	0.03
	VMF	OR = 1.32 (0.64-2.73)	0.4
	Shape	OR = 16.14 (6.77-38.47)	<0.0001
	Color	OR = 2.18 (1.52-3.12)	<0.0001
	Side	OR = 1.08 (0.66-1.76)	0.8
Feature win-stay x group (referenced to controls)	Shape x DMF	OR = 0.34 (0.10-1.19)	0.09
	Shape x LLF	OR = 0.12 (0.04-0.34)	<0.0001
	Shape x RLF	OR = 0.38 (0.08-1.71)	0.2
	Shape x VMF	OR = 0.29 (0.09-0.90)	0.03
	Color x DMF	OR = 0.81 (0.47-1.38)	0.4
	Color x LLF	OR = 2.49 (0.83-7.48)	0.1
	Color x RLF	OR = 0.78 (0.49-1.24)	0.3
	Color x VMF	OR = 1.08 (0.66-1.79)	0.7
	Side x DMF	OR = 2.02 (0.73-5.57)	0.2
	Side x LLF	OR = 5.13 (1.64-16.02)	0.005
	Side x RLF	OR = 0.48 (0.22-1.03)	0.06
	Side x VMF	OR = 1.11 (0.59-2.10)	0.7

Similarly, we tested if subjects with frontal lobe damage differed from controls in the probability of switching away from a shape, color or side after a choice was paired with the absence of reward (i.e. 'no-win'-shift behavior; Figure 3.4B). The full results of this GEE can be found in Table 3.5. We found no differences between controls and any frontal lobe damaged groups in this behavior for either the relevant shape dimension, or in the irrelevant color, or side dimensions. Thus, groups differed principally in their tendency to stay with previously rewarded features in this task.

Table 3.5. Odds ratios (OR), 95% confidence intervals (CIs) and respective *P* values for trial-by-trial no win-shift behavior for all three dimensions.

	Effect	**OR (95% CI)**	***P* value**
Main Effects	Intercept	OR = 1.20 (0.83-1.75)	0.3
	DMF	OR = 1.43 (0.86-2.39)	0.17
	LLF	OR = 0.83 (0.49-1.40)	0.5
	RLF	OR = 1.30 (0.69-2.44)	0.4
	VMF	OR = 0.90 (0.57-1.44)	0.7
	Shape	OR = 1.01 (0.65-1.58)	0.9
	Color	OR = 0.94 (0.81-1.10)	0.5
	Side	OR = 0.50 (0.33-0.75)	0.0009
Feature no win-shift x group (referenced to controls)	Shape x DMF	OR = 0.75 (0.35-1.64)	0.5
	Shape x LLF	OR = 0.97 (0.60-1.57)	0.9
	Shape x RLF	OR = 1.14 (0.54-2.43)	0.7
	Shape x VMF	OR = 0.86 (0.53-1.42)	0.6
	Color x DMF	OR = 1.31 (1.01-1.71)	0.04
	Color x LLF	OR = 1.53 (0.84-2.78)	0.2
	Color x RLF	OR = 0.98 (0.76-1.28)	0.9
	Color x VMF	OR = 1.05 (0.78-1.42)	0.7
	Side x DMF	OR = 0.59 (0.31-1.12)	0.1
	Side x LLF	OR = 1.01 (0.49-2.07)	0.9
	Side x RLF	OR = 0.59 (0.26-1.33)	0.2
	Side x VMF	OR = 1.09 (0.62-1.92)	0.7

Recent choice history

We were interested in whether the influence of feedback on choices of irrelevant features depended on accumulated feature-reward history, or were driven primarily by highly local (i.e. one trial back) feature-reward pairings. We tested how the frequency of rewards (positive feedback), or lack of rewards (negative feedback), associated with recent choices of relevant and irrelevant stimulus features affected current decisions. We separately calculated the relative frequency of positive feedback and negative feedback for stimulus features comprising the left and right decision options in each trial, based on choices in the past four trials. We then used a GEE model to estimate the probability of subjects choosing the left option as a function of the relative frequency of positive and

negative feedback associated with stimulus features on the left and right in all three stimulus dimensions.

We first fit this model in the control subjects to test the effects of reward history in each stimulus dimension. There were significant effects for the difference in positive feedback frequency for left and right shapes (OR = 1.52, CI: 1.37-1.71, $P < 0.0001$), and left and right colors (OR = 1.14, CI: 1.07-1.22, $P < 0.0001$), but not the left or right sides (OR = 1.01, CI: 0.97-1.06, $P = 0.5$). Healthy controls' choices were unaffected by the relative frequency of negative feedback for left and right shapes (OR = 0.94, CI: 0.85-1.05, $P = 0.3$), or colors (OR = 0.99, CI: 0.95-1.03, $P = 0.7$), however these subjects showed a small, but consistent, tendency to avoid choosing a side that was more frequently associated with negative feedback (OR = 0.90, CI: 0.85-0.95, $P = 0.0001$). Thus, control subjects chose shapes and colors associated with a greater frequency of reward and avoided sides that had been frequently unrewarded in past choices, similar to the pattern of behavior revealed by the trial-by-trial analysis.

We next tested the interaction of group status with the history of positive (reward) and negative (absence of reward) feedback for each of these stimulus dimensions. The full results of this analysis can be found in Table 3.6. The relative frequency of positive, but not negative, feedback for the relevant shapes had a weaker influence on the choices of DMF, LLF and VMF groups compared to controls, but not the RLF group (Figure 3.5A). No frontal lobe damaged group was affected more than controls by the relative frequency of positive feedback history of the irrelevant colors (Figure 3.5B), though the DMF group showed a marginally significant tendency to choose colors associated with more frequent negative feedback, compared to controls (Figure 3.5E). Notably, the LLF group alone was more likely

than controls to make choices based on the frequency of positive feedback associated with the left and right sides (Figure 3.5C). The RLF group was significantly less likely to choose the side with a greater frequency of either positive or negative feedback (Figure 3.5C,F), essentially switching away from a side repeatedly chosen over several trials. Post-hoc tests on these coefficients between frontal damaged groups revealed a significant difference between RLF and LLF groups in the influence of the difference in reward frequency for the left and right sides ($P = 0.009$, Bonferroni-corrected t-test), and no other significant differences in the influence of positive and negative feedback history. Thus, the LLF group was influenced more by the reward history of the irrelevant side dimension, while VMF, DMF and LLF groups were all less sensitive than controls to the history of positive feedback within the relevant (shape) dimension.

Table 3.6. Odds ratios (OR), 95% confidence intervals (CIs) and respective *P* values for effects of the difference in reward history of features in the left and right options.

	Effect	**OR (95% CI)**	***P* value**
Main Effects	Intercept	OR = 0.17 (0.08-0.34)	<0.0001
	DMF	OR = 2.11 (0.66-6.73)	0.2
	LLF	OR = 0.42 (0.08-2.15)	0.3
	RLF	OR = 2.34 (0.58-9.43)	0.2
	VMF	OR = 1.30 (0.52-3.24)	0.6
	Shape reward	OR = 1.53 (1.37-1.71)	<0.0001
	Color reward	OR = 1.14 (1.07-1.22)	<0.0001
	Side reward	OR = 1.01 (0.97-1.06)	0.5
	Shape no reward	OR = 0.95 (0.85-1.06)	0.3
	Color no reward	OR = 0.99 (0.95-1.04)	0.7
	Side no reward	OR = 0.90 (0.86-0.95)	0.0001
Feature positive reward history x Group (referenced to controls)	Shape reward x DMF	OR = 0.84 (0.71-0.99)	0.04
	Shape reward x LLF	OR = 0.75 (0.64-0.88)	0.0004
	Shape reward x RLF	OR = 0.93 (0.76-1.15)	0.5
	Shape reward x VMF	OR = 0.84 (0.72-0.97)	0.02
	Color reward x DMF	OR = 0.98 (0.87-1.10)	0.7
	Color reward x LLF	OR = 1.16 (0.96-1.40)	0.1
	Color reward x RLF	OR = 0.97 (0.88-1.07)	0.5
	Color reward x VMF	OR = 1.00 (0.91-1.09)	0.9
	Side reward x DMF	OR = 1.08 (0.99-1.17)	0.1
	Side reward x LLF	OR = 1.25 (1.10-1.43)	0.0006
	Side reward x RLF	OR = 0.90 (0.83-0.97)	0.01
	Side reward x VMF	OR = 1.03 (0.95-1.11)	0.5
Feature negative reward history x Group (referenced to controls	Shape no reward x DMF	OR = 1.01 (0.87-1.17)	0.9
	Shape no reward x LLF	OR = 1.06 (0.95-1.19)	0.3
	Shape no reward x RLF	OR = 1.10 (0.92-1.30)	0.3
	Shape no reward x VMF	OR = 1.02 (0.90-1.16)	0.8
	Color no reward x DMF	OR = 1.08 (1.00-1.16)	0.04
	Color no reward x LLF	OR = 1.10 (0.93-1.31)	0.2
	Color no reward x RLF	OR = 1.02 (0.95-1.09)	0.6
	Color no reward x VMF	OR = 1.02 (0.96-1.09)	0.5
	Side no reward x DMF	OR = 0.87 (0.74-1.01)	0.07
	Side no reward x LLF	OR = 0.95 (0.81-1.12)	0.6
	Side no reward x RLF	OR = 0.89 (0.82-0.97)	0.008
	Side no reward x VMF	OR = 1.00 (0.93-1.07)	0.9

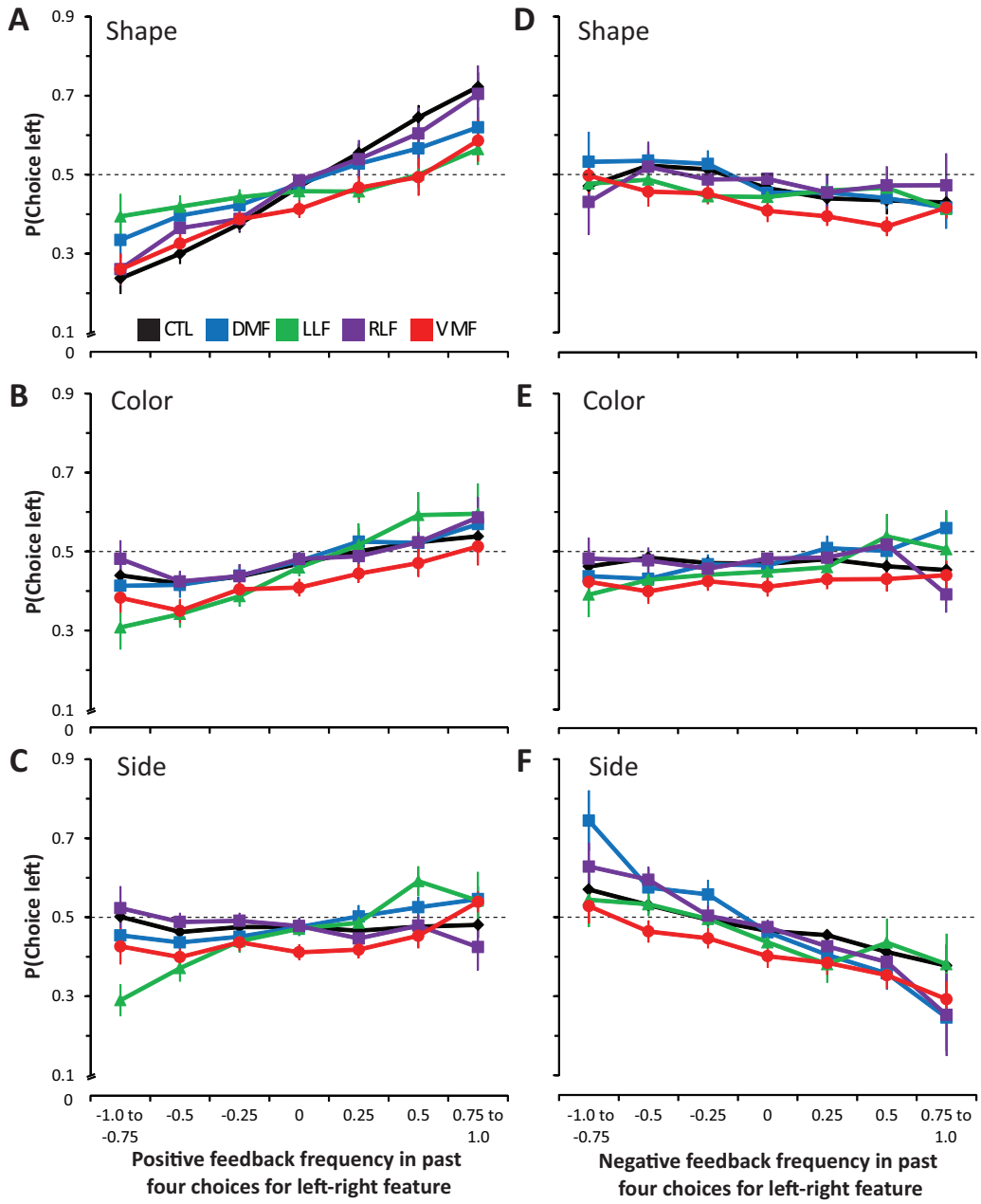

Figure 3.5. Influence of recent feedback history within each stimulus dimension on choice. **A-C**. Probability of choosing the left item as a function of the relative frequency of positive feedback for past choices of the left and right **A.** shape, **B.** color and **C.** side. **D-F**. Probability of choosing the left item as a function of the relative frequency of negative feedback for past choices of the left and right **A.** shape, **B.** color and **C.** side.

Feature information and learning

Theories of associative learning in multidimensional settings suggest that attention helps sculpt learning by focusing on features that are informative about feedback contingencies (Mackintosh, 1975; Pearce & Hall, 1980). While subjects were explicitly instructed about which stimulus dimension was informative, all groups, including healthy controls, were sensitive to the recent feedback history of features within ultimately uninformative stimulus dimensions. Although these irrelevant dimensions were not predictive, they may have gained some apparent information value through spurious correlation with rewards in subsets of trials. We sought to test if subjects' trial-by-trial attribution of feedback to the relevant or irrelevant stimulus dimensions depended on the apparent information value within these dimensions based on recent feedback history, and if sensitivity to information value within relevant and irrelevant dimensions was affected by frontal lobe damage.

We first tested if trial-by-trial performance in healthy control subjects was affected by the information in each stimulus dimension. The information in each dimension was calculated as the absolute value of the difference in the frequency with which each feature was associated with reward in the past four choices. This measure captured the extent to which the relative value of features in each dimension carried apparent information about reward associations based on recent trial history. We used separate GEE models to test how the probability of staying with a previously rewarded shape, color and side was affected by the information in each dimension. Once again, we first tested these effects in controls to assess the extent to which information in each dimension affected reward attribution in healthy subjects. With greater information in the shape dimension, healthy controls stayed with previously winning shapes significantly more often (OR = 1.44, CI:

1.32-1.58, $P < 0.0001$), and previously winning colors significantly less often (OR = 0.90, CI: 0.84-0.97, $P = 0.006$). Information in the shape dimension did not affect the likelihood of controls choosing the previously rewarded side (OR = 0.95, CI: 0.89-1.03, $P = 0.2$), which was unsurprising given that these subjects were not overall inclined to choose the previously rewarded side, as described earlier. Similarly, healthy controls did not choose a previously winning side more, even as the side dimension became more informative (OR = 1.06, CI: 0.99 -1.12, $P = 0.1$). Nor did the information in the side dimension affect the probability of sticking with a rewarded color (OR = 1.00, CI: 0.95-1.05, $P = 0.9$), or shape (OR = 1.00, CI: 0.90-1.02, $P = 0.2$). Similarly, control subjects did not stick with a rewarded color more as this dimension became more informative (OR = 1.06, CI: 0.97-1.14, $P = 0.2$). However, as the color dimension became more informative, these subjects were less likely to stick with the rewarded shape (OR = 0.86, CI: 0.80-0.92, $P < 0.0001$), though the probability of choosing a rewarded side was unchanged (OR = 0.96, CI = 0.91-1.02, $P = 0.2$). Thus, healthy control subjects scaled the extent to which feedback was attributed to stimulus features based on the information value in both relevant and irrelevant stimulus dimensions, derived from recent reward history.

We next examined how frontal lobe damage affected the influence of information in relevant and irrelevant stimulus dimensions on reward attribution. GEE models were used to test the interaction between group status and reward information on win-stay behavior in all three dimensions. In win-stay behavior for the relevant shape dimension (Table 3.7), the LLF group showed a trend toward less influence from information in the relevant shape dimension.

Table 3.7. Odds ratios (OR), 95% confidence intervals (CIs) and respective *P* values for the influence of information in the relevant and irrelevant dimensions on the probability of staying with a previously rewarded shape.

	Effect	**OR (95% CI)**	***P* value**
Main Effects	Intercept	OR = 2.71 (1.75-4.19)	<0.0001
	DMF	OR = 0.64 (0.36-1.14)	0.1
	LLF	OR = 0.40 (0.24-0.66)	0.0004
	RLF	OR = 0.58 (0.27-1.26)	0.2
	VMF	OR = 0.61 (0.37-1.03)	0.06
	Shape information	OR = 1.45 (1.33-1.58)	<0.0001
	Color information	OR = 0.86 (0.80-0.92)	<0.0001
	Side information	OR = 0.95 (0.90-1.02)	0.2
Feature win-stay x group (referenced to controls)	Shape information x DMF	OR = 0.89 (0.76-1.04)	0.2
	Shape information x LLF	OR = 0.84 (0.70-1.01)	0.07
	Shape information x RLF	OR = 0.95 (0.80-1.13)	0.6
	Shape information x VMF	OR = 0.92 (0.79-1.06)	0.2
	Color information x DMF	OR = 1.14 (0.98-1.33)	0.08
	Color information x LLF	OR = 1.01 (0.98-1.22)	0.1
	Color information x RLF	OR = 1.06 (0.96-1.18)	0.2
	Color information x VMF	OR = 1.07 (0.97-1.19)	0.2
	Side information x DMF	OR = 0.95 (0.84-1.06)	0.3
	Side information x LLF	OR = 1.03 (0.88-1.20)	0.7
	Side information x RLF	OR = 1.10 (1.00-1.21)	0.06
	Side information x VMF	OR = 0.96 (0.86-1.06)	0.4

We next examined win-stay behavior for the irrelevant color dimension (Table 3.8). The LLF group was significantly more influenced by information in this dimension compared to controls. However, post-hoc tests revealed no significant difference between frontal damaged groups in the influence of color information (*P*'s > 0.1, Bonferroni corrected t-tests). There was also a slight trend for the LLF group to stick with a winning color less as reward information in the side dimension increased.

Table 3.8. Odds ratios (OR), 95% confidence intervals (CIs) and respective *P* values for the influence of information in the relevant and irrelevant dimensions on the probability of staying with a previously rewarded color.

	Effect	**OR (95% CI)**	***P* value**
Main Effects	Intercept	OR = 1.40 (1.15-1.7)	0.0007
	DMF	OR = 0.99 (0.72-1.37)	0.9
	LLF	OR = 1.84 (0.83-4.11)	0.1
	RLF	OR = 0.98 (0.71-1.33)	0.9
	VMF	OR = 1.09 (0.83-1.43)	0.5
	Shape information	OR = 0.90 (0.84-0.97)	0.006
	Color information	OR = 1.06 (0.97-1.15)	0.2
	Side information	OR = 1.00 (0.95-1.05)	0.9
Feature win-stay x group (referenced to controls)	Shape information x DMF	OR = 1.08 (0.96-1.21)	0.3
	Shape information x LLF	OR = 0.89 (0.71-1.11)	0.3
	Shape information x RLF	OR = 1.10 (0.99-1.21)	0.07
	Shape information x VMF	OR = 1.01 (0.91-1.12)	0.8
	Color information x DMF	OR = 0.90 (0.79-1.02)	0.1
	Color information x LLF	OR = 1.15 (1.01-1.30)	0.03
	Color information x RLF	OR = 0.92 (0.81-1.03)	0.1
	Color information x VMF	OR = 1.03 (0.93-1.15)	0.5
	Side information x DMF	OR = 0.99 (0.89-1.11)	0.9
	Side information x LLF	OR = 0.87 (0.74-1.03)	0.1
	Side information x RLF	OR = 0.96 (0.88-1.04)	0.3
	Side information x VMF	OR = 0.98 (0.92-1.05)	0.6

As in the color dimension, LLF damaged subjects showed greater win-stay behavior for the rewarded side as information in this dimension increased, compared to control subjects (Table 3.9). However, as information in the color dimension increased, this group chose the rewarded side less often. Similarly, the DMF group chose the rewarded side less often as information in the relevant shape dimension increased. Post-hoc tests revealed no significant differences between frontal lobe damaged groups in the influence of information for any of these dimensions on the probability of staying with a rewarded side (*P*'s > 0.1, Bonferroni corrected t-tests).

Table 3.9. Odds ratios (OR), 95% confidence intervals (CIs) and respective *P* values for the influence of information in the relevant and irrelevant dimensions on the probability of staying with a previously rewarded side.

	Effect	**OR (95% CI)**	***P* value**
Main Effects	Intercept	OR = 1.07 (0.81-1.43)	0.6
	DMF	OR = 1.59 (0.90-2.82)	0.1
	LLF	OR = 1.82 (1.00-3.31)	0.05
	RLF	OR = 0.62 (0.34-1.14)	0.1
	VMF	OR = 0.97 (0.69-1.36)	0.9
	Shape information	OR = 0.95 (0.89-1.03)	0.2
	Color information	OR = 0.97 (0.92-1.02)	0.2
	Side information	OR = 1.06 (0.99-1.13)	0.1
Feature win-stay x group (referenced to controls)	Shape information x DMF	OR = 0.86 (0.75-1.00)	0.04
	Shape information x LLF	OR = 1.03 (0.89-1.18)	0.7
	Shape information x RLF	OR = 1.09 (0.97-1.23)	0.1
	Shape information x VMF	OR = 1.03 (0.94-1.14)	0.5
	Color information x DMF	OR = 1.02 (0.90-1.16)	0.7
	Color information x LLF	OR = 0.85 (0.77-0.94)	0.001
	Color information x RLF	OR = 1.04 (0.93-1.17)	0.5
	Color information x VMF	OR = 0.95 (0.87-1.02)	0.2
	Side information x DMF	OR = 1.03 (0.92-1.16)	0.6
	Side information x LLF	OR = 1.27 (1.09-1.49)	0.002
	Side information x RLF	OR = 1.01 (0.88-1.16)	0.9
	Side information x VMF	OR = 1.13 (0.97-1.33)	0.1

Overall, the LLF group alone was more inclined to attribute rewards to features in irrelevant dimensions as the information value of these dimensions increased. This group was also more likely to switch between attributing rewards to the irrelevant side or color dimensions, depending on the information value of these dimensions extracted from recent trials.

Reaction times

We anticipated that the random switching of the color and side of the relevant shapes might result in trial-by-trial interference effects reflected in choice reaction times. Indeed, we found that subjects were slower to choose a previously rewarded shape when it

changed colors ($F_{(1,56)} = 4.07$, $P = 0.05$), or sides ($F_{(1,56)} = 42.66$, $P < 0.0001$), on the next trial. There was also a significant interaction between side and color repetition ($F_{(1,56)} = 14.44$, $P = 0.0004$), with larger effects of color repetition when the previously chosen shape stayed on the same side. However, there was no significant effect of group ($F_{(4,56)} = 0.91$, $P = 0.5$), nor any interaction between group and color or side repetition (F's $_{(4,56)} \leq 1.04$, P's ≥ 0.4), nor three-way interaction between color and side repetition with group ($F_{(1,56)} = 0.93$, $P = 0.4$; Figure 3.6). Thus, changes in the color or side of a shape significantly affected RT when choosing a previously rewarded shape, and this effect was similar between groups.

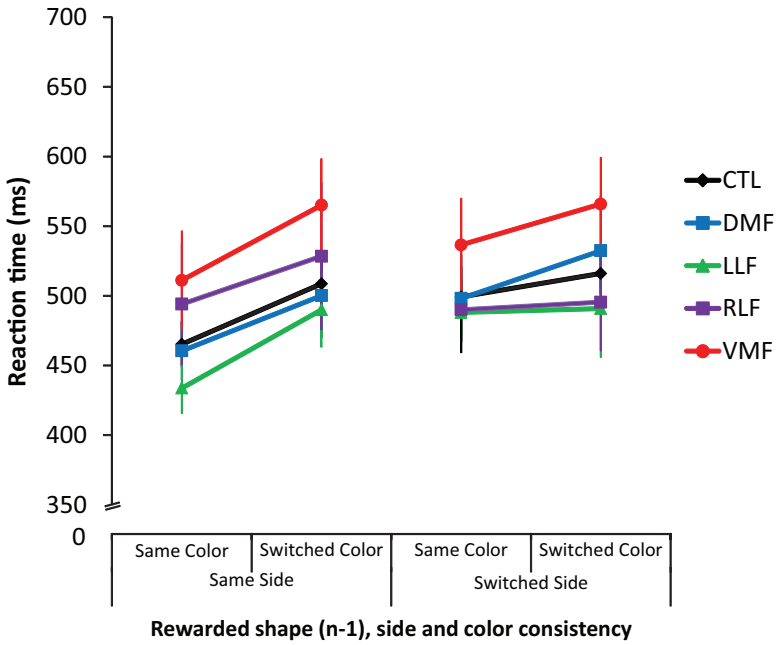

Figure 3.6. Influence of trial-by-trial changes in irrelevant stimulus dimensions on reaction times for choosing a previously rewarded shape.

Psychoactive medication

The proportion of patients taking psychoactive medication was not evenly distributed across lesion groups (see Methods). To test for any effects of psychoactive medication on task performance, we used a GEE model to test the effects of medication in patients, collapsed across group and medication type, on the influence of difference of

positive and negative feedback history in each of the three stimulus dimensions (see below). We found no significant difference between patients on and off psychoactive medication on the influence of positive feedback history for the shape (OR = 0.98, CI: 0.86-1.11, *P* = 0.7), color (OR = 0.92, CI: 0.82-1.10, *P* = 0.7) or side (OR = 0.99, CI: 0.89-1.11, *P* = 0.9) dimensions. Similar results were found for the influence of negative feedback history in these stimulus dimensions (shape: OR = 0.99, CI: 0.90-1.08, *P* = 0.8; color: OR = 0.93, CI: 0.85-1.01, *P* = 0.09; side: OR = 0.97, CI: 0.87-1.07, *P* = 0.5).

Voxel-based lesion symptom mapping

The above analyses focus on differences in learning between healthy controls and frontal lobe damaged subjects, grouped according to relatively coarse anatomical regions of interest. We followed up on these findings with voxel-based lesion symptom mapping (VLSM), which is not constrained by predefined anatomical boundaries, and can provide insights into whether more narrowly defined sub-regions are driving the effects. This method compares the behavior of subjects with damage at each voxel to all other lesioned subjects in the sample.

Multiple logistic regression analyses were used to estimate parameters for individual subjects' win-stay behavior in each stimulus dimension. Given that VLSM removes the age and education matching designed into the primary region-of-interest analyses, we first tested if parameters for win-stay behavior in each of these stimulus dimensions were related to age or education in the healthy control group using multiple linear regression. A significant positive relationship was found between parameters for win-stay behavior in the shape dimension and education level (OR = 2.50, CI: 1.56-4.00, *P* = 0.002), but not age (OR = 1.00, CI: 0.97-1.03, *P* = 0.9). Neither education level (OR = 0.80, CI:

0.39-1.63, $P = 0.6$), nor age (OR = 1.02, CI: 0.96-1.07, $P = 0.4$) was related to parameters for win-stay behavior in the color dimension. Education level was modestly associated with parameters for win-stay behavior in the side dimension (OR = 2.30, CI: 1.15-4.58, $P = 0.02$), though age was not (OR = 1.03, CI: 0.98-1.08, $P = 0.2$). To correct for these relationships, we calculated the residuals of coefficients for win-stay behavior in the shape and side dimensions in frontal lobe damaged patients by subtracting the values predicted by age and education level based on the healthy control group. No correction was applied to coefficients for win-stay behavior for the irrelevant color dimension, as this measure was unrelated to these demographic variables.

Figure 3.7A shows the voxels where there was sufficient lesion overlap to test for lesion-performance relationships using VLSM, and the power to detect significant effects (i.e. maximum detectable z-score based on Wilcoxon non-parametric tests, as in Glascher et al. (2009)). No voxels passed the permutation corrected threshold for significance at $P < 0.05$ for win-stay behavior in the shape dimension ($Z > 3.35$), or for win-stay behavior in the side dimension ($Z > 3.43$). However, increased win-stay behavior for the color dimension was significantly associated with damage in the left inferior frontal gyrus in two clusters of voxels ($Z = 3.72$, $P = 0.001$, permutation corrected; Figure 3.7B). We also explored effects at the uncorrected threshold for significance ($Z > 1.92$, two-tailed). The coordinates and Z scores for all clusters of voxels above this uncorrected threshold can be found in Table 3.10.

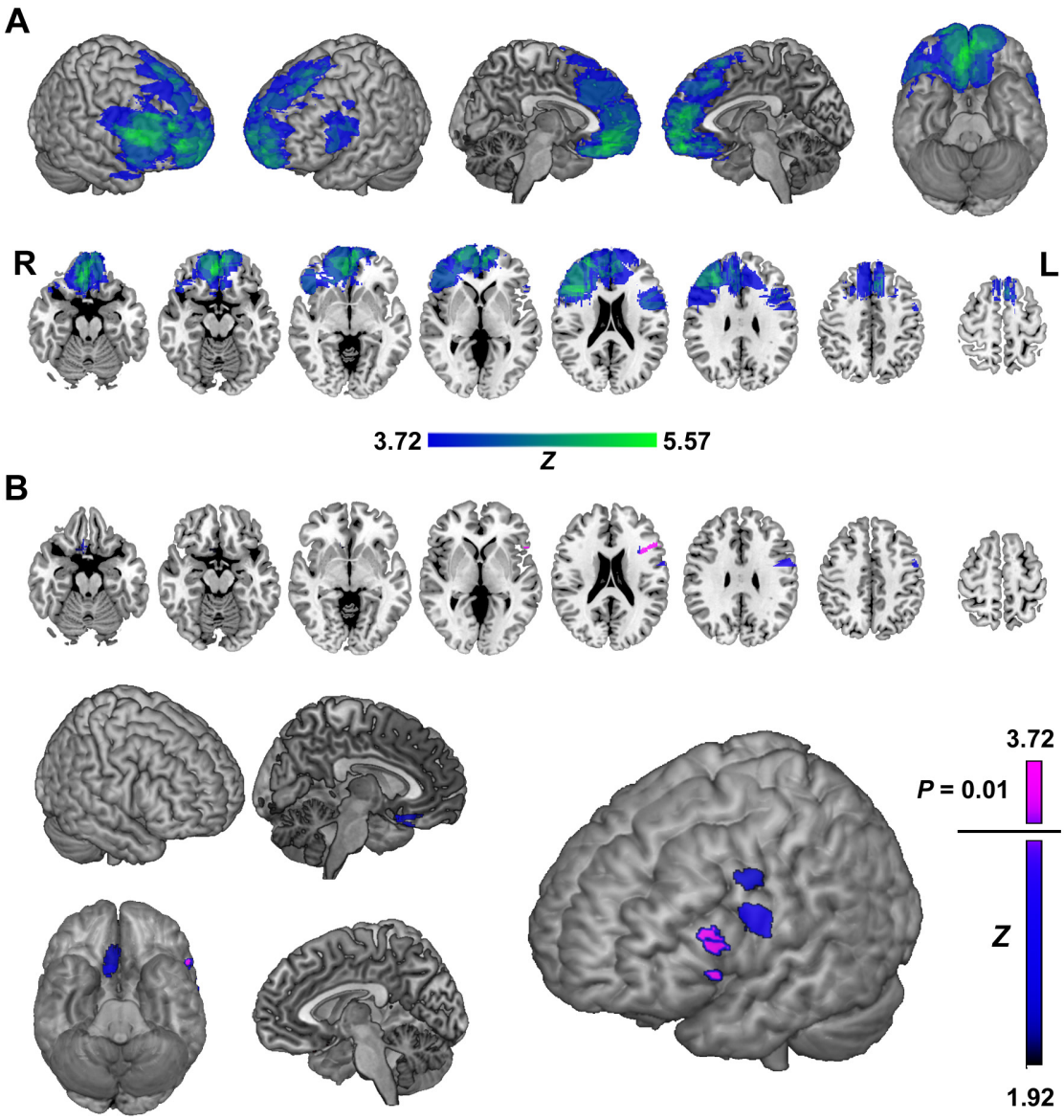

Figure 3.7. Voxel-based lesion symptom mapping (VLSM) analysis. **A.** Power map of voxels with sufficient lesion overlap for VLSM methods. The color scale indicates the maximum possible *Z*-score detectable at a given voxel, an indication of the power for detecting effects. Top row shows this map overlaid on the MNI brain in three-dimensional views, bottom row shows representative axial slices. Numbers above the axial slices correspond to z-coordinates in MNI space. R, Right L, Left. **B.** VLSM statistical map for increased win-stay behavior in the color dimension overlaid on MNI brain in axial slices (top) and three-dimensional views (bottom). Color scale indicates Brunner-Munzel *Z* scores. Voxels in pink represent where significant effects were found at $P = 0.01$, permutation corrected.

Table 3.10. Coordinates of regions associated with decreased win-stay behavior within the relevant shape dimension, and increased win-stay behavior within the irrelevant color and side dimensions.

	Region	Hemisphere	x	y	z	BM Z maximum	Number of voxels
Shape	Superior frontal gyrus	Left	-17	13	50	2.42	337
	Supplementary motor area	Left	-13	15	63	2.42	217
	Superior frontal gyrus white matter	Right	19	53	7	2.03	118
	Superior frontal gyrus	Right	24	58	1	2.03	184
	Middle frontal gyrus	Right	25	56	3	2.03	62
Color	Inferior frontal gyrus pars triangularis	Left	-54	19	0	3.72	326
	Inferior frontal gyrus pars opercularis	Left	-48	13	13	3.72	168
	Precentral gyrus	Left	-55	-1	21	2.97	1262
	Postcentral gyrus	Left	-65	-1	20	2.97	243
	Superior orbital gyrus	Right	11	17	-21	2.69	109
	Olfactory cortex	Right	4	14	-18	2.69	249
	Gyrus rectus	Right	6	16	-21	2.69	665
Side	Supplementary motor area	Left	-14	1	64	3.09	1007
	Suplementary motor area white matter	Left	-15	-3	57	2.96	930
	Superior frontal gyrus	Left	-18	-4	69	2.96	921
	Precentral gyrus	Left	-17	-4	69	2.96	296
	Medial orbitofrontal cortex	Left	0	57	-13	2.63	126
	Gyrus rectus	Left	-1	47	-19	2.63	421
	Middle frontal gyrus	Left	-34	19	31	2.53	103
	Inferior frontal gyrus pars opercularis	Left	-34	17	32	2.53	3664
	Insula	Left	-32	13	18	2.41	329
	Inferior frontal gyrus pars triangularis	Left	-40	20	30	2.40	1190
	Medial superior frontal gyrus	Left	-4	20	43	2.38	452
	Anterior cingulate	Left	-8	36	11	2.08	191
	Postcentral gyrus	Left	-65	-1	16	1.97	159
	Rolandic operculum	Left	-61	10	6	1.97	462

Region labels are taken from the automated anatomical labeling template (Tzourio-Mazoyer et al., 2002). Coordinates indicate the maximum value for each cluster in MNI space. BM Z scores greater than 2.58 are significant at $P < 0.01$ (uncorrected) and greater than 1.92 at $P < 0.05$ (uncorrected).

Discussion

Here, we tested the necessary contributions of four frontal lobe sub-regions to reward learning in a multidimensional environment where only one dimension was predictive of feedback. We focused on the interaction of attention and learning, examining how relevant and irrelevant reward associations influenced trial-by-trial behavior. LLF damaged subjects showed the greatest impairments in this task, with deficits in learning about the relevant stimulus dimension and an increased tendency to make choices based on rewards associated with a second, irrelevant dimension. Subjects with VMF damage were also impaired in staying with the relevant stimulus dimension, but were not more influenced by the feedback history within irrelevant dimensions compared to controls. These distinct behavioral patterns argue that these frontal sub-regions have different functional roles in optimally navigating a multidimensional task environment.

The impairment of LLF damaged patients in this task was surprising given the intact performance of such patients in simpler dynamic reward learning tasks (Fellows & Farah, 2003; Tsuchida et al., 2010). However, stimulus options were more complex and rapidly presented than in those studies, stressing top-down, selective attention. Importantly, the impairment of the LLF group could not be explained by a simple perseverative bias to a rewarded side or color, as these subjects took into account the recent history of feedback within these irrelevant dimensions in their choices., The LLF group was also not completely insensitive to the history of feedback in the relevant dimension, and decreased their win-stay behavior in the irrelevant dimensions when reward history in the relevant dimension was more informative. Thus, LLF damaged subjects appeared to discriminate these stimuli, but failed to attribute feedback to the appropriate dimension.

Attentional learning theories argue that the locus of attention determines the strength of learned stimulus-reward relationships (Kruschke, 2003), and that outcomes can be easily attributed to salient, but irrelevant, stimuli (Mackintosh, 1976; Pavlov, 1927). The mirror shapes used here were less discriminable, and likely less visually salient, than the colors or side of the stimulus, taxing selective attention. The deficits of the LLF group are consistent with impairment in selectively attending to the relevant, but non-salient, shape dimension and ignoring salient distractors, resulting in the misattribution of rewards. This functional explanation is closely analogous to this region's putative contribution to selective attention in other settings, like visual search (Buschman & Miller, 2007; Suzuki & Gottlieb, 2013; Tremblay et al., 2015), and the classic Stroop task (Glascher et al., 2012; Perret, 1974; Tsuchida & Fellows, 2013).

These findings have relevance to current theories of lateral PFC function. Our findings provide causal support for the work of Niv et al. (2015), arguing that the frontoparietal attention network, including lateral PFC, facilitates the selection of stimulus dimensions for feedback attribution. In addition to misattributing rewards, LLF damaged subjects also showed a greater tendency to fluctuate between attributing rewards to irrelevant color and side features depending on local correlations with feedback. This increased sensitivity to local changes in the apparent information value within these irrelevant dimensions might reflect a reduction in attentional filtering (Chrysikou, Weber, & Thompson-Schill, 2014). Recent imaging studies in humans and monkeys have argued that interactions between anterior ventrolateral PFC and the amygdala mediate the fidelity of feedback attribution (Chau et al., 2015; Jocham et al., 2016). Future work studying the

connections necessary for appropriate feedback attribution might shed further light on the brain networks involved in multidimensional learning of this kind.

The nature of the stimuli used here might also be relevant to the current findings. Mirror letter stimuli are specially processed by the left hemisphere (Nakamura, Makuuchi, & Nakajima, 2014; Pegado, Nakamura, Cohen, & Dehaene, 2011), and left hemisphere lesions sometimes affect reading and writing of mirror letters (Schott, 2007). LLF patients therefore may have had particular difficulty tuning attention to the letter-shaped stimuli. Further work is necessary to establish if lateral PFC has lateralized, material–specific contributions during associative learning, as we have shown in more conventional cognitive control tasks (Geddes et al., 2014). Relevant and irrelevant features were also perceptually bound together as single objects, requiring subjects to take a dimensional approach that generalized across stimuli. The object-level presentation of these options might have encouraged attention to irrelevant features (O'Craven, Downing, & Kanwisher, 1999), and also incidental learning about irrelevant dimensions. The binding of these features might therefore have placed greater demands on lateral frontal dependent attentional processes.

In contrast, we did not find evidence that VMF lesions affected the attribution of feedback to irrelevant stimulus dimensions compared to controls. Thus, learning deficits in VMF damaged subjects are likely not the result of 'distracted' learning due to misattribution of feedback to irrelevant features. This result is in line with work demonstrating that VMF damage does not affect the ability to select between stimulus dimensions, or ignore irrelevant, salient features in conventional attention tasks, such as

the Stroop task (Glascher et al., 2012; Tsuchida & Fellows, 2013), or ignore changes in irrelevant stimulus dimensions in an associative learning task (Chase et al., 2008).

We observed impaired learning within the relevant dimension in the VMF group, consistent with other work suggesting this region facilitates attention to reward predictive stimuli (Chase et al., 2008; Vaidya & Fellows, 2015). The current results are in line with a role for VMF in tuning attention to reward predictive stimulus features within this relevant dimension, as well as recent imaging studies suggesting that VMF facilitates choosing previously rewarded options (Boorman, Rushworth, & Behrens, 2013), and attributing outcomes to stimuli that are perceived to be predictive (Akaishi, Kolling, Brown, & Rushworth, 2016). Notably, VMF damaged subjects in this study did not differ from controls in scaling reward attribution based on the information value of the relevant and irrelevant features. However, compared to controls, their choices were influenced less by the accumulated evidence from reward history within the relevant dimension. These results suggest that VMF damage may affect the ability of subjects to direct attention within stimulus dimensions that are ultimately predictive of rewards in the long-term, but not based on local changes in the apparent information value of stimulus dimensions.

DMF damaged subjects showed a trend toward attributing rewards to the irrelevant side, and decreased sensitivity to the history of positive feedback in the relevant dimension. The VLSM analysis indicated that left DMF damage affected these measures more than right DMF damage, suggesting some commonality with the LLF group, possibly related to common damage to underlying white matter. As in most real-life situations, the side of the stimulus (i.e. left or right side of the screen) was completely correlated with the action needed to acquire it (i.e. left or right button). Prior work has shown that DMF

damage in monkeys and humans impairs learning about the value of actions from feedback in action selection tasks without visual stimuli (Camille, Tsuchida, et al., 2011; Rudebeck, Behrens, et al., 2008). Increased win-stay behavior for previously chosen actions is, at a glance, counterintuitive given this previous work, though staying with previously rewarded, but non-predictive, actions could itself be a sign of impaired action-value learning. However, it is impossible to distinguish spatial- or action-based accounts for this behavior in the current dataset.

In this task, subjects were verbally instructed regarding the relevant dimension. This prior information likely mitigated against greater attention to irrelevant stimulus dimensions. Learning about the information value in each stimulus dimension may be especially important when subjects are forced to use evidence from reward history to infer which dimensions are relevant based on feedback (Pearce & Mackintosh, 2010). Future work addressing how focal brain damage affects learning in a completely uninstructed multidimensional task will be helpful for establishing the neural mechanisms involved in forming an attentional set *de novo* based on reward feedback.

As with all studies of patients with brain damage, lesions are not under experimenter control. While only patients with well-characterized, focal lesions were included in this study, lesion damage may affect both cortex and underlying white matter, including fibers of passage. Rudebeck et al. (2013) have argued that learning impairments associated with OFC damage in macaques may relate to the interruption of such fibers. We cannot rule out such a possibility here, though VLSM analysis could, in principle, reveal if behavioral deficits were associated with a consistent pattern of white matter damage. As

with any method, converging evidence from other techniques will be important to fully address these limitations.

In summary, we examined the effects of frontal lobe damage on learning about reward-predictive and irrelevant stimulus dimensions in a dynamic environment. The findings argue that, within the frontal lobes, selective attention processes dependent on LLF become critical under these more naturalistic conditions, in contrast to the narrow reliance on the VMF sub-region when learning from probabilistic reward predicted by consistent stimuli. A complete understanding of value-based learning must address not only how reward is assigned to relevant predictors, but also how irrelevant features are suppressed. This work is a contribution to this effort, and suggests a framework for relating well-studied aspects of lateral PFC function to models of value-related behavior centered on the VMF.

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Chapter 4: Dorsomedial, and not ventromedial, frontal lobe damage affects fixation-based value updating

Preface

The past two chapters focused on frontal lobe contributions to directing attention to reward-predictive stimulus features, or dimensions, and how attention helps to shape learning. Other work has argued that attention, as measured through visual fixations, can also influence choices between naturalistic stimuli based on subjective value (Krajbich et al., 2010; Krajbich & Rangel, 2011; Shimojo et al., 2003). Ventromedial PFC has been suggested to have a role in this bias (Lim et al., 2011), but the underlying neural mechanisms remain little studied. In this third study, published in Nature Communications, we demonstrate that damage to ventromedial and lateral frontal lobes did not affect the influence of visual fixations on choice. However, dorsomedial frontal damage increased the influence of fixation time on choice.

Testing necessary regional frontal contributions to value assessment and fixation-based updating*

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Abstract

Value-based decisions are biased by the time people spend viewing each option: Options fixated longer are chosen more often, even when previously rated as less appealing. This bias is thought to reflect "value updating" as new evidence is accumulated. Prior work has shown that ventromedial prefrontal cortex (PFC) carries a fixation-dependent value comparison signal, while other studies implicate dorsomedial PFC in representing the value of alternative options. Here, we test whether these regions are necessary for fixation-related value updating in 33 people with frontal lobe damage and 27 healthy controls performing a simple choice task. We show that damage to dorsomedial PFC leads to an exaggerated influence of fixations on choice, while damage to ventromedial or lateral PFC has no effect on this bias. These findings suggest a critical role for dorsomedial, and not ventromedial PFC, in mediating the relative influence of current fixations and *a priori* value on choice.

Introduction

Traditional theories of economic decision-making argue that a rational actor makes choices guided by a comparison of the utility (or subjective value) of available options, leading to internally consistent choices (Samuelson, 1938; von Neumann & Morgenstern, 1944). However, humans make decisions more flexibly, expressing a variety of biases. Recent studies have shown that visual fixations influence value-based choices: subjects choose options they have looked at longer more often than would be predicted by their *a priori* value ratings of those options alone (Krajbich et al., 2010; Krajbich, Lu, Camerer, & Rangel, 2012; Krajbich & Rangel, 2011; Towal et al., 2013). This bias is present even when the duration of fixations is experimentally manipulated (Armel et al., 2008; Shimojo et al., 2003). These findings argue that decisions do not rely only on a comparison of the pre-determined values of options, but are also influenced by information gathered "in the moment" through fixations.

We know very little about the neural processes underlying this dynamic value updating. However, regions within the frontal lobes have been implicated in value-based choice more generally. Activity within ventromedial PFC reflects the subjective value of available options (Bartra et al., 2013; Kable & Glimcher, 2007; Padoa-Schioppa & Assad, 2006; Rangel, 2013), and predicts choice (Tusche, Bode, & Haynes, 2010). Patients with damage to this region and adjacent orbitofrontal cortex (OFC) (together termed ventromedial frontal lobe; VMF) are more internally inconsistent when making preference-based choices (Camille, Griffiths, et al., 2011; Fellows & Farah, 2007; Henri-Bhargava et al., 2012). Macaques with medial OFC lesions fail to update the value of visual cues in selective satiety paradigms (Rudebeck & Murray, 2011b). These findings have together been taken

as evidence that VMF represents and compares options in a common value currency (Kable & Glimcher, 2009; Padoa-Schioppa & Assad, 2006; Rangel & Clithero, 2013).

Dorsomedial frontal (DMF) regions have also been linked to value processing and decision-making. Dynamic value-related signals have been reported within this region in fMRI and electrophysiology studies, and linked to choice, particularly in foraging contexts (Bartra et al., 2013; Kolling et al., 2012; Quilodran et al., 2008). Lesions to this region in humans and macaques lead to impairment in optimal action-value learning (Camille, Tsuchida, et al., 2011; Rudebeck, Behrens, et al., 2008), but whether this region is critical for decision-making under more ecologically valid conditions remains unclear.

Neural representations of value are dynamically modulated as a decision is prepared. Correlates of accumulating value information have been found in PFC prior to choice, suggesting that values are constructed in this region during the decision process (Harris, Adolphs, Camerer, & Rangel, 2011; Hunt et al., 2012; Lim et al., 2013; Philiastides et al., 2010; Polania, Krajbich, Grueschow, & Ruff, 2014). Lim et al. (2011) showed that hemodynamic signals reflecting relative value in PFC were dependent on which option the subject looked at when choosing between foods, arguing that these value computations were influenced by fixations. However, whether these signals are necessary for value updating during decision-making has not been established.

Here, we test the causal role of three PFC sub-regions in this fixation-driven dynamic value updating. Patients with damage to ventromedial (VMF), dorsomedial (DMF) or lateral frontal (LF) lobes, and age-matched healthy control subjects judged how much they wanted a variety of artworks, and then chose between pairs of these artworks while we tracked their eye movements. As in prior studies with this paradigm, subjects' choices

are biased by fixations. DMF damage leads to an exaggerated influence of fixations on choice, while VMF and LF damaged subjects perform normally in this, and most other aspects of the task.

Methods

Subjects

Patients with focal lesions involving the frontal lobes (N=33) were recruited from the Cognitive Neuroscience Research Registry at McGill University (Fellows et al., 2008). They were eligible if they had a fixed lesion primarily affecting the frontal lobes. They were tested a minimum of 5 months after the injury (median, 4.76 years after; range: 5 months to 48 years). Twelve patients were taking psychoactive medications: 8 were taking anticonvulsants, 5 were taking anti-depressants, and 2 were taking anxiolytics. There was no significant difference in the frequency of psychoactive medication use between PFC groups (Chi-square test of independence: $c^2 = 2.65$ (2), $P = 0.3$). A power analysis of pilot data collected from healthy young subjects was used to inform the determination of group sample size.

Age- and education-matched healthy control subjects (N =27) were recruited through local advertisement in Montreal. They were free of neurological or psychiatric disease and were not taking any psychoactive drugs. They were excluded if they scored 26 or less on the Montreal Cognitive Assessment (Nasreddine et al., 2005). Mean performance was 28.1, $SD = 1.4$.

Two subjects (one control and one VMF damaged patient) were excluded from the study because they did not rate enough artworks above ‘0’ to generate trials for the choice task. Another VMF patient was excluded because she only used ‘0’ and the extremes of the

value scale ('-3' and '3'), making it impossible to generate trials with the same value rating differences as other subjects. One DMF patient was excluded because there was residual tumor evident on imaging, so that the extent of the lesion could not be characterized with confidence. One patient with LF damage was excluded as she failed to understand the task instructions.

All subjects provided written, informed consent in accordance with the Declaration of Helsinki and were paid a nominal fee for their time. The study protocol was approved by the McGill University Research Ethics Board.

Lesion analysis

Individual lesions were traced from the most recent clinical computed tomography or magnetic resonance imaging onto the standard Montreal Neurological Institute (MNI) brain using MRIcro software (Rorden & Brett, 2000) (freely available at www.mccauslandcenter.sc.edu/mricro/) by a neurologist experienced in imaging analysis and blind to task performance. A related software tool (MRIcron) was used to generate lesion overlap images and estimate lesion volumes. Patients were separated into groups based on the location of damage by this same neurologist. The grouping of subjects conformed to broad divisions of the PFC used in neuropsychological studies of PFC damage (Stuss et al., 2005; Szczepanski & Knight, 2014). One patient in the DMF group had a second lesion in the parietal lobe. This patient's fixation bias was not driving the group effect (normalized fixation bias: 0.10). Another patient in the VMF group also had damage in the parietal white matter, but again, this patient's behavior was not notably different from the rest of the VMF group (normalized fixation bias: -1.17). DMF lesions were due to tumor resection in 10 cases, aneurysm rupture in 1 case and hemorrhagic stroke in 1 case.

Lesions in the LF group were caused by ischemic stroke in 5 cases and tumor resection in 3 cases. Lesions affecting VMF were attributable to tumor resection in 9 cases, aneurysm rupture in 3 cases, and hemorrhagic stroke in 1 case.

Neuropsychological screening

All patients underwent neuropsychological screening to assess cognitive functions more generally, to detect deficits that might affect experimental task performance for other reasons. Hemispatial neglect was tested with the Posner cueing task (Posner, 1980), and a circle cancellation task (Marsh & Hillis, 2008). Patients also completed a task that tested visual memory for faces without explicit instructions (incidental memory) (Bower & Karlin, 1974), two tests of verbal fluency, a well established index of left frontal function (Fluency-F, Animals) (Benton et al., 1989), a test of working memory (backwards digit span) (Lezak et al., 2012), and a test of the ability to understand and follow 1, 2 and 3-step verbal instructions (sentence comprehension, similar to the Token Test (Derenzi & Vignolo, 1962)).

Apparatus

All experimental tests were programmed using E-Prime 1.2 (Psychology Software Tools, Inc., Pittsburgh, PA, USA). Subjects' heads were stabilized using a headrest and stimuli were presented on a 19-inch monitor (Dell Inc., Round Rock, TX, USA) positioned approximately 57 cm from their eyes. Monocular recordings of the movement of each subject's dominant eye were acquired at 1000 Hz using an Eyelink 1000 system with a desk-mounted camera (SR Research Ltd., Mississauga, Ontario, Canada).

Rating tasks

Subjects completed two separate rating tasks, one where they were asked to judge how much they wanted the presented artwork, and a second control task where they were asked to judge the brightness of a separate set of artwork. The artwork was sampled from a wide range of styles and periods, and included pieces from both famous and lesser-known artists. The diversity of artworks presented to subjects was intended to encompass the idiosyncrasies of individual preferences. In both tasks, we tested the consistency of subjects' responses by asking subjects to judge a subset of the artwork again for both value and brightness at the end of the testing session. The purpose of this retest phase was to establish whether patients' rating of the value of artwork was stable over time, and to determine whether any inconsistency was specific to value ratings.

Subjects were first asked to rate how much they wanted to have 175 individual pieces of artwork on a scale of -3 to 3. On each trial, a central fixation cross was presented for 500 ms. Subjects would then see the artwork in the center of the screen, as well as a prompt above the artwork reading 'How much do you want this artwork?' The scale was presented below the artwork, with labels below -3 ("Not at all"), 0 ("Indifferent") and 3 ("Very much.") Subjects would verbally report a number to the experimenter, who would then click the corresponding number using a computer mouse. The first 125 artworks presented to subjects in the rating task were used to generate pairs of artwork for the choice task (see below). The remaining 50 artworks were presented to subjects again after the choice task in the retest phase. The order of artwork presentation was randomized for every subject.

After the first rating task, subjects were asked to judge the brightness of a separate set of 50 artworks. These artworks covered the same wide range of subject matter and

style as the set in the first test, and also varied considerably in mean luminance. The format of this task was nearly identical to the first rating task. In each trial, subjects were presented with a central artwork, and a prompt reading "How bright is this artwork?" Subjects rated each artwork on a scale of -3 to 3 by reporting a number to the experimenter. Labels appeared below -3 ("Very dull"), 0 ("Neutral") and 3 ("Very bright.") Subjects were again asked to judge the brightness of these same 50 artworks at the end of the experiment during the retest phase. All subjects reviewed the instructions for each task with the experimenter before starting each test. In the brightness rating task, subjects were specifically instructed to rate artwork for perceptual brightness rather than mood of the artwork.

Choice task

The design of the choice task was very similar to that used by Krajbich et al. (2010). A custom made Matlab (Mathworks, Natick, MA, USA) script sorted the first 125 artworks presented to subjects in the value rating task into pairs for the choice task. Similar to Krajbich et al. (2010), any artworks that subjects had rated below '0' (i.e. artworks they did not want) were excluded from the choice task. The script selected pairs of artworks based on the difference in subjects' ratings, with three levels (0, 1 or 2). There were 34 pairs for each difference level in the choice task (102 pairs total). This script also ensured that no artwork appeared more than 8 times during the course of the task.

Subjects were instructed to choose which artwork they wanted more from each of the presented pairs. Subjects were told that they would receive a copy of one of the artworks they chose at the end of the experiment to provide an incentive for answering

honestly. Subjects received a postcard-sized copy of the artwork they chose in the final trial of this task. This trial was not included in any analysis.

All subjects completed a 13-point eye-tracker calibration sequence covering a 32.1 by 26.6° area before beginning the task. On each trial, subjects had to hold fixation on a central fixation cross for 500 ms before the trial began. This process also served to ensure the quality of calibration throughout the test: Failure to maintain fixation in a 1.6 by 1.8° box around the fixation cross would cause the fixation slide to repeat. After three consecutive failures, the eye-tracker would be recalibrated. After holding central fixation, subjects were presented with two artworks on either side of the screen (the side of the artworks was randomized with respect to their ratings). Subjects were allowed to freely inspect the artwork for an indefinite period before finally making a choice by pressing the left- or right-most keys of a serial response box (Psychology Software Tools, Inc., Pittsburgh, PA, USA) to choose the artwork on the corresponding side. After making a choice, the selected artwork was highlighted with a yellow border for 1,000 ms. Subjects then saw a blank screen for 1,000 ms before the start of the next trial.

Eye-tracking analysis

Fixations were defined using the online parser of the Eyelink 1000: saccades were identified using a velocity threshold of 30° per second, an acceleration threshold of 8,000° per second squared and a distance threshold of more than 0.15°. This same parser also automatically rejected blinks. In-house written Matlab (Mathworks, Natick, MA, USA) scripts were used to determine the location of fixations and extract the data for analysis. Trials where subjects did not make a fixation to either option were rejected from further analysis (0.21% of all trials).

Choice task analysis

Fixations were defined as a set of continuous eye movements made to either option, and fixation shifts were defined as fixations where the subject shifted eye position from one option to the other. The number of fixation shifts measured how many times subjects broke their fixation from one option to look at another during the course of a trial. The middle fixation time was calculated as the average duration of all fixations that fell between the first fixation and last fixation on any given trial, as in Krajbich et al. (2010). This usage of the term 'fixation' is consistent with prior studies using this paradigm (Krajbich et al., 2010; Krajbich & Rangel, 2011), though it is somewhat different from the definition typically used in the eye-movement literature.

Fixation time advantage was calculated by taking the difference of the total time subjects spent fixating the left and right option by the end of the trial (at the point where the subject made a choice). To assess how fixation advantage influenced choice, trials were binned based on this measurement. The size of these bins was set to ensure that trials were relatively well distributed among bins (mean number of trials in each bin: less than -500 ms (M = 17.0, SD = 9.0), -500 to -150 ms (M = 20.9, SD = 6.6), -150 to 150 ms (M = 26.1, SD = 10.0), 150 to 500 ms (M = 20.0, SD = 5.7), more than 500 ms (M = 17.8, SD = 8.8)).

Saliency analysis

Saliency maps were calculated for all artworks used in the choice task using the SaliencyToolbox, an open-access Matlab (Mathworks, Natick, MA, USA) tool for evaluating the saliency of computer images based on simple visual features (Walther & Koch, 2006). The default toolbox parameters were used, where color, orientation and intensities were all equally weighted (weight = 1.0). The sum of the saliency maps were computed for each image as in Towal et al. (2013). As this measure was negatively correlated with the area of

the image (non-parametric Spearman Rho correlation: $\rho = -0.437$, $p < 0.0001$), we corrected each saliency estimate for the area of the image based on this linear correlation to obtain a more accurate estimate. Trials were then classified based on whether the estimated visual saliency of the left or right option was higher.

Comparison of effects between hemifields

The effects of fixation advantage and value ratings were compared for options presented in the contra- or ipsilesional hemifields. This analysis could only be completed in 25 patients where damage was restricted to one hemisphere. The influence of value ratings in each hemifield was tested by comparing the frequency subjects chose options with a higher value rating when presented contra- or ipsilesionally. Similarly, the effect of fixation advantage was tested by comparing the frequency subjects chose the option fixated for longer when presented in the contra- or ipsilesional hemifield. This measure was corrected for the value rating difference of the options by subtracting the frequency subjects chose the fixation-advantaged option, given their value rating difference, from subjects' choice of the fixation-advantaged option (0 or 1) in each trial, as in Krajbich et al. (2010).

Attentional drift diffusion model

The attentional drift diffusion model (aDDM) was fit to individual subject data to test whether the effects of prefrontal damage on task performance could be systematically related to changes in the parameters of this model. This model was originally described by Krajbich et al. (2010), and is based on the drift diffusion model developed by Ratcliff (1978). In the aDDM, binary choices are modeled as a stochastic diffusion process moving between two equidistant barriers reflecting the instantaneous relative decision value (RDV). When the process crosses the barrier set by the threshold, a decision is made. A

unique feature of this model is that the direction of this process depends on the locus of fixation, such that when fixations are made to the left, the diffusion process changes at every time point according to $RDV_t = RDV_{t-1} + d(V_{left} - \theta V_{right}) + s$, and when fixations are made to the right according to $RDV_t = RDV_{t-1} - d(V_{right} - \theta V_{left}) + s$. Here, V_{left} and V_{right} represent the value ratings of the left and right options, respectively, and the parameter θ represents the fixation discount rate on the range of 0 to 1. The parameter d is the drift constant, governing the rate of integration. The parameter s represents the variability in the drift rate and acts as a scaling parameter. Here, s was set to a constant (0.1) multiplied by Gaussian white noise randomly sampled every time step.

Within the model, the RDV was sampled every 10 ms in simulated trials based on the equations described above. In each simulated trial, the location of the first fixation was based empirically on the frequency the subject looked left or right first in all trials. The duration of each fixation was randomly sampled from the maximum likelihood estimate of the lognormal distribution of the subject's fixation times to the side of fixation at each level of value difference for the left and right options (-2, -1, 0, 1, 2). Model reaction times were computed from the time the RDV crossed the threshold, plus the 'non-decision time,' calculated from the empirical mean time to the first fixation. As each fixation is considered instantaneous in the model, a transition time was added to the RT for each simulated fixation. Transition times were randomly sampled from the maximum likelihood estimate of the lognormal distribution of subjects' empirical transition times.

We fit the model to all trials for each subject. While this approach risks over-fitting the model to the data and prohibits cross-validation, it was necessary to allow even an exploratory analysis, given the small number of trials in the experiment. For each

simulation, 12,000 trials were generated for each subject. The composition of trial conditions was directly based on the proportion of trials in each condition in each subject's data (i.e. same proportion of trials where the left option was rated '3' and the right option was rated '1', etc.).

The model was fit using Kolmogorov-Smirnov equations, based on the method of Voss, Rothermund, and Voss (2004). Subject and simulated data were split into three conditions based on the absolute value difference of the options (0, 1, 2). Given the low number of trials, we collapsed across left and right side, as we did not find any systematic bias toward choice of a particular side in any group. All reaction times were included in a single distribution for each condition; with choices of the low value option assigned a negative sign (for trials with a value difference of zero, choices of the left option were arbitrarily negative signed). Outlier RTs (outside the 0.005 and 0.995 quantiles of the RT distribution) were removed from the subject data and simulated trials to improve the fit of the model. For each condition, the fit of the simulation to the subject's data was assessed using the Kolmogorov-Smirnov test. The objective function for the model fitting procedure was the sum of the negative natural logarithm of the *P*-values from these three tests. Model parameters were fit using the pattern search algorithm in the Matlab global optimization toolbox (Mathworks, Natick, MA, USA). The theta parameter was constrained to the range of 0 to 1, the drift constant to a range of 0.001 to 0.05, and the threshold parameter to a range of 0.75 to 4.0. For each subject, the model fitting procedure was run 10 times, 9 times at random initialization points and once from a fixed, centered point. The set of parameters that best minimized the objective function were then selected for each subject.

Rating consistency analysis

To adjust for individual differences in rating anchoring, and in the range of the scale utilized, the brightness and value ratings of artworks used in the test-retest phases were normalized. Ratings were converted into Z-scores based on the means and standard deviations of subjects' ratings of these options in each phase. The mean absolute difference of the normalized ratings of these artworks was then calculated for each subject to measure rating consistency.

The relationship between fixation bias and value rating consistency was tested in healthy controls using a multiple linear regression model that incorporated age and education as nuisance variables, as they were found to correlate with fixation bias in simple regression analyses. We computed a single index of fixation bias based on the difference in the probability subjects chose the left option when they spent more time fixating the left or right option. To remove the influence of the value difference of options on choice, we corrected subjects' choices of the left option (0 or 1) by subtracting the average frequency the subject chose the left option given the value rating difference of the options in each trial as in Krajbich et al. (2010). The fixation bias index was calculated from the difference in this corrected probability of choosing the left option for trials where there was a greater fixation advantage to the left or the right. Control subjects' fixation bias was converted to a z-score based on the mean and standard deviation of the group to standardize the coefficients. Education was incorporated as an ordinal variable with three levels (high school or less, some undergraduate education to undergraduate degree, some graduate education to graduate degree).

To determine if differences between groups were an artifact of age, education or value rating inconsistency, we calculated the residuals of fixation bias not accounted for by

these variables in all subjects. The fixation bias index was calculated for all subjects and normalized with reference to the mean and standard deviation of the control group. We then calculated the predicted normalized fixation bias for each subject based on the coefficients from the multiple linear regression model These predicted values were subtracted from the observed normalized fixation bias to yield a residualized fixation bias measure (i.e. variance in fixation bias not accounted for by age, education and value rating inconsistency).

Behavior-based lesion analysis

The Non-Parametric Mapping (NPM, version June 6, 2013) software (freely available at www.mccauslandcenter.sc.edu/mricro/npm/) was used for voxel-based lesion symptom mapping (VLSM) analysis. The residuals of the fixation bias index were used in the VLSM analysis. Voxel-wise comparisons between patients were carried out using non-parametric Brunner-Munzel (BM) tests (Brunner & Munzel, 2000) in all voxels where there were three or more patients with lesion damage. To control for multiple comparisons, a null distribution of BM *Z*-scores was calculated from the same dataset using permutation tests (3000 permutations) (Nichols & Holmes, 2002). This method provides an assumption-free means of controlling for multiple comparisons that is also more powerful than commonly used corrections like the Bonferroni method (Kimberg et al., 2007). This test yielded a threshold of $Z > 3.35$ (for $P < 0.05$) and $Z > 3.48$ (for $P < 0.025$). Images of the results of this analysis were created using the software MRICron.

Statistical analysis

Mixed measures ANOVAs were used to examine the effect of value differences on subjects' fixation properties and reaction times, and to compare groups. Non-parametric

Kruskal-Wallis tests were used to test for group differences in value and brightness rating consistency, as well as model parameters. Post-hoc between-subjects *t*-tests, or non-parametric Mann-Whitney U-tests, were carried out to test for specific differences between groups where group effects were present. The alpha level of all post-hoc tests was corrected for multiple comparisons between groups using the Bonferroni method where all pair-wise tests were completed, (α=0.0083, for P = 0.05).

Mixed measures ANOVAs were also used to test for differences in responses to options presented in the contra- and ipsilesional hemifields in patients with unilateral damage. Post-hoc between subject *t*-tests were used to compare between patient groups, with an alpha level corrected using the Bonferroni method (α=0.017, for P = 0.05).

Given that fixation advantage was influenced by the rating difference of options, we corrected for this effect by calculating a measure of fixation advantage that was not predicted by differences in the saliency or rating difference of options. We used multiple linear regression in each subject to calculate a 'predicted fixation advantage' for each trial based on the rating difference of these options and whether the left option was more salient. We then subtracted the predicted fixation advantage for the left option from the observed fixation advantage in each trial to obtain fixation advantage residuals that were used in all relevant analyses.

Generalized estimating equations (GEEs), as implemented in SAS (version 9.4, SAS Institute Inc., Cary, NC, USA) were used to examine subjects' choice behavior. This analysis is very similar to multiple linear regression, but takes account of the correlation of responses within subjects. Choice of the left option as a binary outcome was modeled as a function of group (a categorical variable referenced to the control group), left-right value

rating difference (an ordinal variable from -2 to 2), fixation advantage to the left versus right option (an ordinal variable with bins for fixation time difference of over 500 ms to the right or left, 150-500 ms more to the right or left, or under 150 ms to either), and saliency difference (a binary variable, greater saliency to the left or right).

Similarly, a GEE was also used to test how fixation bias was influenced by subjects' value ratings. Choice of the option with a greater fixation advantage (binary outcome) was modeled as a function of group (again, referenced to controls), the rating difference of the fixation-advantaged option and the alternative (an ordinal variable from -2 to 2), the magnitude of fixation advantage (an ordinal variable from less than 150 ms, 150-500 ms, or more than 500 ms), and saliency (a binary variable, greater for fixation-advantaged option or alternative).

In both analyses, we started with a simple GEE model including main effects for each of these variables and then systematically added interactions between each variable and group to test if lesion damage altered the influence of these variables on choice. The optimal model was selected based on the minimum Quasi-Akaike Information Criterion (QIC), which balances fit of the model (based on the maximum likelihood function) with number of parameters. Supplementary table 4.1 provides the QIC statistics for each model and the associated Akaike weights. These weights indicate the relative likelihood of each model based on the QIC statistics. A single odds ratio (OR) and 95% confidence interval was computed for each variable, as well as each interaction.

To compare ratings of value and brightness for artworks between the control group and patient groups, we computed the average rating for each artwork in the initial rating task within each group. We then used non-parametric Spearman correlations to test

whether the average brightness and value ratings for artworks given by the patient groups followed a similar pattern to the average ratings given by controls.

Code availability

Computer code used in the analysis of data presented here is available upon request.

Results

People with focal lesions involving the frontal lobes (N=33) and healthy older controls (N=27) were recruited from the Cognitive Neuroscience Research Registry at McGill University. PFC patients were divided *a priori* into three subgroups, (VMF, DMF and LF), based on the location of their damage, assessed on their most recent MRI or CT imaging by a neurologist blind to task performance, according to standard boundaries (Stuss et al., 2005). Figure 4.1 shows an overlap image of lesion tracings manually registered to the MNI brain by the same neurologist. Demographic information and lesion volumes are provided in Table 4.1, and neuropsychological screening results in Table 4.2. Performance on attention and executive function tests, and the frequency of use of psychoactive medications, was comparable across patient groups. The DMF group scored lower than the VMF group on a test of incidental memory, and both VMF and DMF groups scored higher than controls on the Beck Depression Inventory-II.

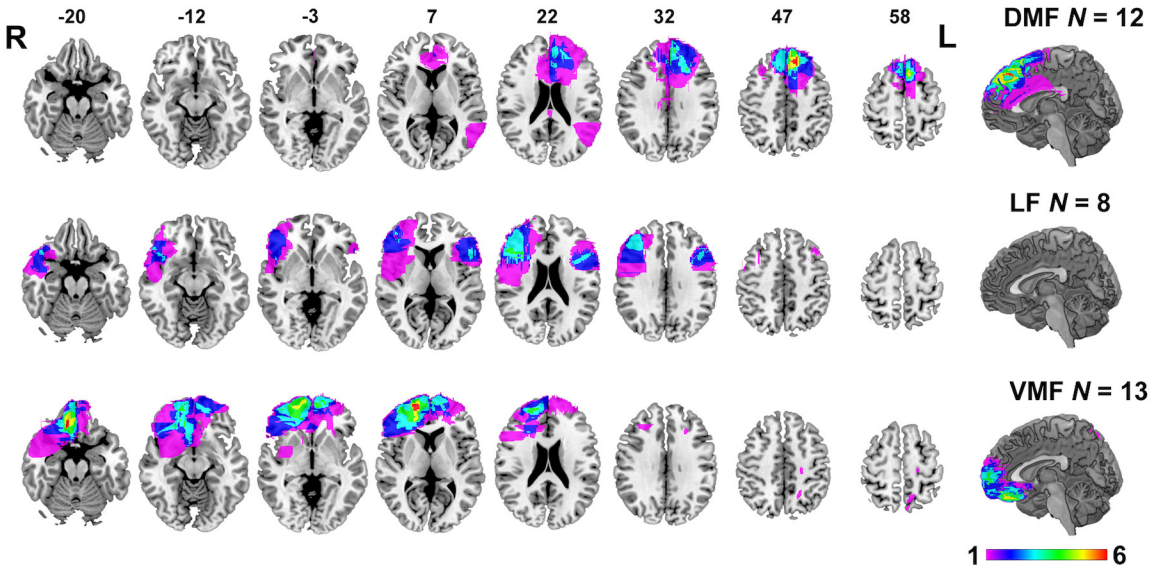


Figure 4.1. Representative axial slices and mid-sagittal view of the MNI brain showing the extent of lesion overlap in the dorsomedial frontal (DMF), lateral frontal (LF) and ventromedial frontal (VMF) groups. Numbers above slices indicate z-coordinates of axial slices in MNI space. Colors indicate extent of lesion overlap, as indicated by the color scale. R, Right; L, Left.

Subjects viewed a set of 175 artworks, one at a time, judging how much they wanted each artwork on a scale of -3 to 3 ('not at all' to 'very much'). A subset of artworks drawn from those rated zero or above were then paired and presented in a binary choice task, similar to Krajbich et al. (2010), with an equal number of trials at each level of rating difference (i.e. 0, 1, 2), while eye movements were tracked. Subjects also rated the brightness of a separate set of 50 artworks on the same scale in a control task. The consistency of ratings was assessed by having subjects re-rate the brightness of these artworks, and the value of 50 artworks from the initial set, not shown in the choice task, at the end of the session.

Table 4.1. Demographic information for controls and prefrontal patients. Values represent means with standard deviations in parentheses, except for lesion volume where the median and range are provided.

Group	Age (years)	Sex (M/F)	Education (years)	BDI-II	AMNART IQ [a]	Lesion Volume (cc)
CTL (N=27)	58.8 (12.9)	9/18	16.4 (3.1)	4.2 (4.9)	121 (5)	-
DMF (N = 12)	54.1 (10.5)	3/9	14.9 (4.1)	10.4 (6.5)*	117 (7)	15 (3-83)
LF (N = 8)	59.5 (9.6)	3/5	15.0 (3.5)	6.3 (6.2)	120 (4)	25 (9-96)
VMF (N = 13)	58.8 (12.0)	5/8	15.8 (2.9)	8.2 (4.9)*	119 (6)	16 (7-77)

[a] Not all subjects were able to complete the AMNART. * $P < 0.05$, two-tailed *t*-test against control scores, uncorrected

Table 4.2. Performance on neuropsychological screening tests for controls and prefrontal patients. Values represent means with standard deviations in parentheses.

Group	Posner Cueing (Uncued-Cued) Left/Right (ms)	Circle cancellation % missed (Left/ Right)	Incidental memory P(Correct)	Fluency - animals	Fluency - F	Backwards Digit Span	Sentence comprehension P(Correct)
CTL (N=27)	57.8 (45.8) 60.5 (38.1)	- -	-	-	-	-	-
DMF (N = 12)	67.5 (57.6) 69.7 (51.8)	0.4 (1.0) 1.1 (2.3)	0.74 (0.15) * [a]	20.0 (8.7) [a]	11.0 (4.7) [a]	2.6 (1.0) [a]	0.98 (0.04) [a]
LF (N = 8)	74.6 (33.9) 65.6 (47.2)	1.2 (1.9) 1.1 (1.8)	0.84 (0.10)	18.9 (7.7)	11.9 (5.9)	2.6 (1.4)	0.93 (0.09)
VMF (N = 13)	82.4 (37.2) 76.0 (40.2)	0.4 (0.9) 1.1 (1.3)	0.87 (0.09)	20.0 (3.8)	10.4 (3.9)	3.3 (1.3)	0.98 (0.06)

[a] Data missing from one patient. * $P < 0.05$, DMF<VMF, two-tailed *t*-test, uncorrected.

Reaction times and fixation properties

We first asked whether PFC damage affected basic aspects of choice task behavior, focusing on the effects of value rating difference on choice RT and eye movements. As the value difference between the two options increased, patients and controls made faster decisions (Mixed measures ANOVA: $F_{2,112} = 25.89$, $P < 0.0001$) (Fig. 4.2a). There was no

significant main effect of group ($F_{3,56}$ = 2.05, P = 0.1), or interaction between group and rating difference ($F_{2,112}$= 0.75 P = 0.6). The same pattern was seen after removing RT outliers (Supplementary Fig. 4.1).

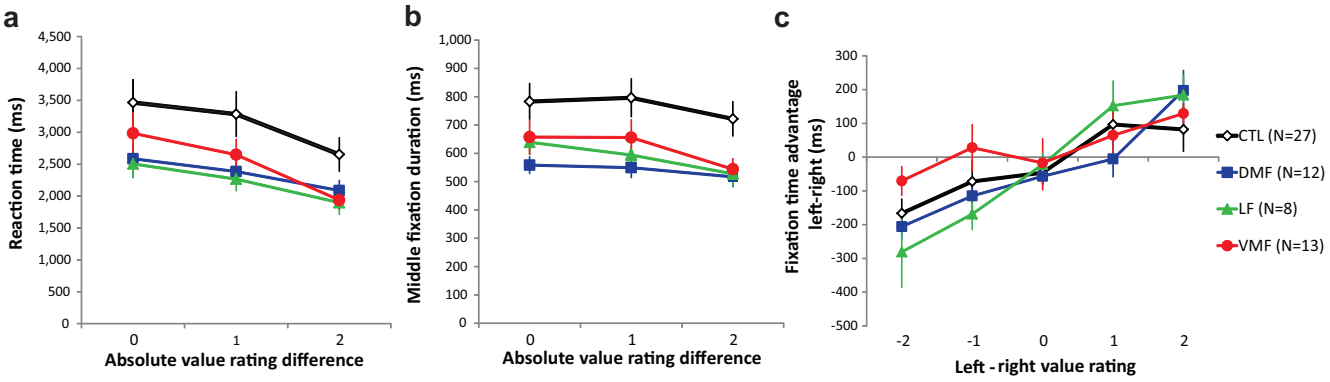


Figure 4.2. Reaction times and fixation properties for the choice task. (**a**) Mean reaction time as a function of the absolute value rating difference of the two options. (**b**) Mean number of fixation shifts between options per trial as a function of the absolute value rating difference of the two options. (**c**) Mean fixation time advantage to the left versus the right option as a function of the value rating difference of the left and right options. White lines show data from control subjects (CTL), blue lines show data from DMF group, green lines show data from LF group and red lines show data from VMF group. Error bars indicate SEM.

In describing eye movements in this task, we use the term 'fixation,' as defined in prior work (Krajbich et al., 2010; Krajbich & Rangel, 2011), to refer to a set of eye movements towards one option before eye position shifted to the opposite option. Subjects shifted fixation between options less often as the value difference between the options increased (Supplementary Fig 4.2). We also examined the average fixation duration between the first and last fixation ('middle fixation duration') during the choice task. Middle fixation duration was shorter as the value rating difference increased (Mixed measures ANOVA: $F_{2,112}$ = 16.57, P < 0.0001), as expected (Krajbich et al., 2010). There was a significant main effect of group ($F_{2,56}$ = 2.95, P = 0.04), but no interaction between group

and value difference on middle fixation duration (Fig. 4.2b*; $F_{6,112} = 1.02$, $P = 0.4$). Post-hoc tests collapsed across value differences showed that middle fixation duration was significantly shorter in all PFC groups compared to controls (Bonferroni corrected *t*-tests: *P*'s ≤ 0.02, two-tailed).

Subjects spent more time fixating highly rated options (Fig. 4.2c), with a significant effect of the value rating difference between the left and right option on fixation advantage (time spent fixating left – right option) (Mixed measures ANOVA: $F_{4,224} = 15.45$, $P < 0.0001$). This tendency was comparable in all groups, with no interaction between value difference and group ($F_{4,224} = 0.87$ $P = 0.6$), or main effect of group ($F_{3,56} = 1.03$, $P = 0.4$).

Analysis of choices

We next asked whether PFC damage changed the relative influence of *a priori* value ratings and 'in the moment' evaluation indexed by fixation time. Generalized estimating equations (GEEs) were used to predict choice of the left option as a binary outcome based on the rating difference of the left and right options, and whether the option was looked at longer (fixation advantage), on individual trials. Rating differences ranged from -2 to 2 (lower to higher rating for left option), while fixation advantage was divided into five bins. Recent work has also shown that visual saliency can bias choices, independent of value (Milosavljevic et al., 2012; Navalpakkam et al., 2010; Towal et al., 2013). We therefore included a binary variable coding which option had greater visual saliency.

Prior work with this task has tested effects of fixation advantage on choice without accounting for the influence of value ratings and saliency on fixations (Krajbich et al., 2010; Krajbich & Rangel, 2011). Both saliency and value can influence fixation times (Towal et al., 2013), posing difficulties for disentangling the effects of these variables. To isolate the

information-gathering process that was the focus of this study, we calculated a 'predicted fixation advantage' based on the *a priori* value rating difference and binary saliency variable for each subject, in each trial. This value was subtracted from subjects' actual fixation advantage, leaving residuals reflecting the fixation advantage not predicted by differences in value ratings and saliency. This variable was used in all further analyses. For consistency with the prior literature, the data were also analyzed using the raw fixation advantage, yielding a very similar pattern of results (Supplementary Fig. 4.3).

Starting with a simple model that only included main effects, we systematically added interactions between group status and each variable. The optimal model was selected based on the minimum Quasi-Akaike Information Criterion (QIC). The tested models and associated QIC statistics are provided in Supplementary Table 4.1. Odds ratios (ORs) and 95% confidence intervals (CIs) are reported for each effect, reflecting the change in probability of choosing the left option as a function of each variable for main effects, and the relative change in this probability in PFC groups compared to controls in the interactions.

The optimal model included interactions of group with rating difference and fixation bias, but not saliency (Fig 4.3 a-c). We found significant main effects of rating difference (OR: 2.79, CI: 2.45-3.19, $P < 0.0001$), fixation advantage (OR: 1.47, CI: 1.37-1.59 $P < 0.0001$) and saliency (OR: 1.16, CI: 1.02-1.32, $P = 0.02$) on choice, replicating previous work (Krajbich et al., 2010; Towal et al., 2013). There were no significant main effects of group (DMF: OR: 1.22, CI: 0.96-1.54, $P = 0.1$; LF: OR: 1.07, CI: 0.74-1.54, $P = 0.7$; VMF: OR: 1.12, CI: 0.92-1.38, $P = 0.2$).

To test if patients made choices that were as consistent with their value ratings as the

control group, we examined the interaction of group with value rating difference (Fig. 4.3a). There was no significant effect for the DMF group (OR: 0.99, CI: 0.78-1.25, $P = 0.9$). However, LF (OR: 1.65, CI: 1.04-2.63, $P = 0.03$) and VMF (OR: 1.24, CI: 1.00-1.53, $P = 0.05$) groups both made choices that were slightly more consistent with their ratings compared to controls.

We also examined the interaction of group with fixation advantage to test if PFC damage affected the influence of fixations on choice (Fig. 4.3b). Fixation advantage has a stronger influence on choice in the DMF group compared to controls (OR: 1.54, CI: 1.18-2.00, $P = 0.001$). In contrast, the effects of fixation advantage on choice in the LF (OR: 1.41, CI: 0.97-2.03, $P = 0.07$) and VMF (OR: 1.09, CI: 0.93-1.28, $P = 0.3$) groups were not significantly different from controls.

One key prediction of previous work with this paradigm is that an increased influence of fixations should be accompanied by decreased sensitivity to the value of the unfixated option (Krajbich et al., 2010). To address this, choices of the fixation-advantaged option were modeled in a separate GEE as a function of the value rating difference of this option and the alternative, with the magnitude of fixation advantage and saliency included as nuisance variables (Fig. 4.3d). Including the interaction of group with rating difference improved the fit over the simple model without interactions (Supplementary Table 4.1). The DMF group was overall more likely to choose the fixation-advantaged option (OR: 1.49, CI: 1.13-1.95, $P = 0.004$), while VMF (OR: 0.98, CI: 0.81-1.21, $P = 0.9$) and LF (OR: 1.17, CI: 0.75-1.83, $P = 0.5$) groups were not significantly different from controls. There was a significant main effect of the value rating difference between the fixation-advantaged and alternative option (OR: 3.15, CI: 2.80-3.55, $P < 0.0001$), as expected. However, the DMF

group was less sensitive to this value rating difference (OR: 0.75, CI: 0.65-0.88, $P = 0.0003$), while VMF (OR: 1.02, CI: 0.90-1.16, $P = 0.7$) and LF (OR: 1.02, CI: 0.73-1.44, $P = 0.9$) groups did not differ from controls. There were also significant main effects of saliency (OR: 1.15, CI: 1.01-1.31, $P = 0.03$), and fixation advantage magnitude (OR: 1.42, CI: 1.28-1.57, $P < 0.0001$). The DMF group's choices were therefore biased toward the fixation-advantaged option, and less sensitive to the value difference between this option and the alternative.

We explored whether patients responded differently to options presented in the contra- or ipsilesional hemifield in the 25 patients with unilateral damage. There were no differences in the effects of fixation advantage, or in the likelihood of subjects choosing the option with a higher value rating for contra- or ipsilesional options, nor did any group preferentially fixate options in either hemifield (Supplementary Fig. 4.4, 4.5).

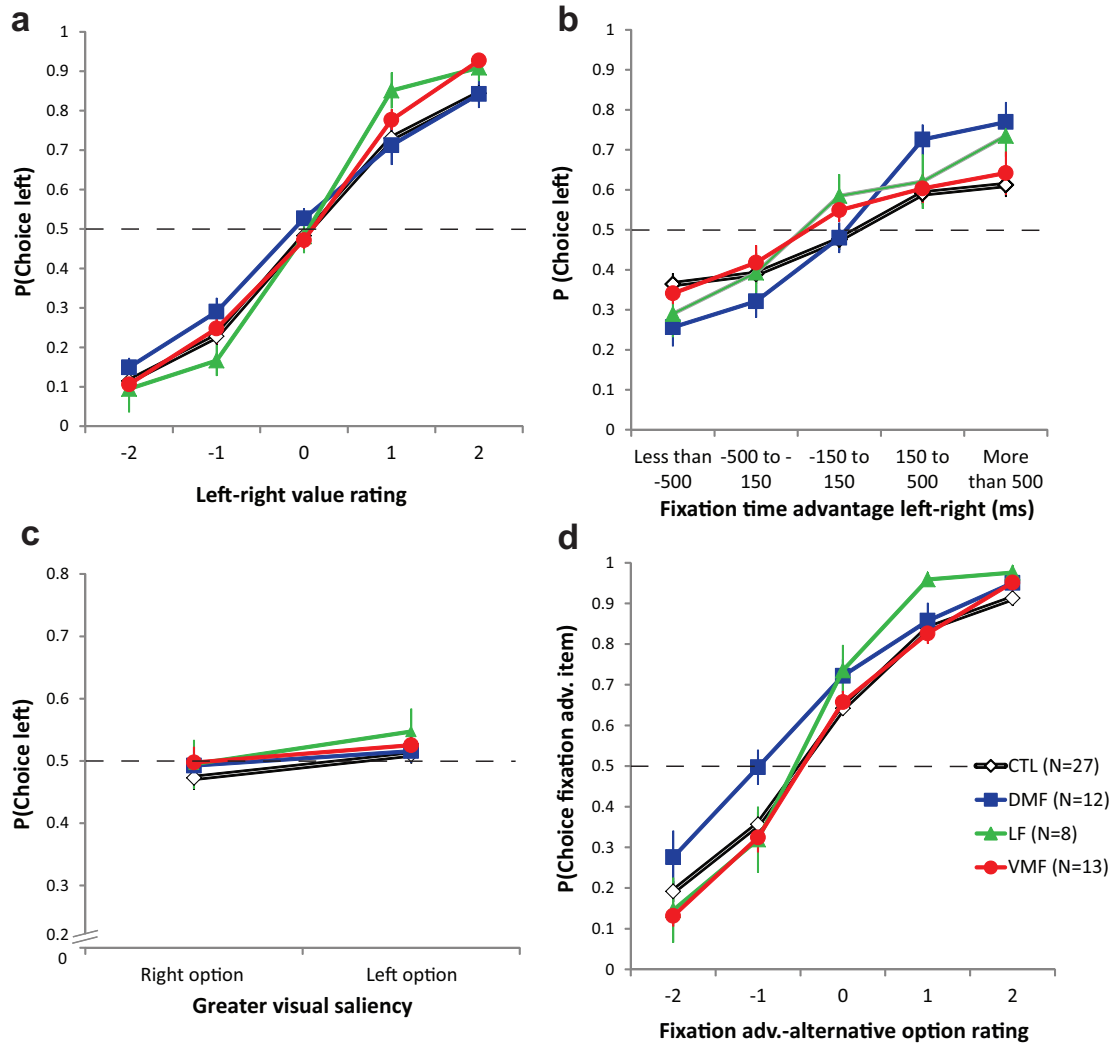


Figure 4.3. Choice properties of each group. (**a**) Probability of choosing the left option as a function of the value rating difference of the left and right option. (**b**) Probability of choosing the left option as a function of fixation advantage to the left versus the right option (c) Probability of choosing the left option as a function of the difference of the visual saliency of the left and right options. (**d**) Probability of choosing the option with a greater fixation advantage as a function of the value rating difference of the fixation-advantaged and the alternative option. Error bars represent the SEM. Dashed line indicates chance probability.

Attentional drift diffusion model

One advantage of this paradigm is that a formal model has been developed that captures several features of the effect of fixations on choice (attentional drift-diffusion model (aDDM) (Krajbich et al., 2010)). In this framework, decisions are modeled as a diffusion process that progresses at a rate dependent on the value difference of available options. Critically, in the aDDM, this rate is weighted by a parameter that discounts the value of the unfixated option, resulting in a bias toward choosing the fixated option. In an exploratory analysis, we fit the model to individual subject data to examine whether the effects of prefrontal damage in this task could be captured by changes in the parameters of this model.

The model included three free parameters: the fixation discount rate, a drift constant that controlled the rate of drift, and a threshold that determined the necessary height of the drift process to trigger a choice (see methods). There was a significant effect of group on the fixation discount rate (Fig 4.4a; Kruskal-Wallis test: $H_3 = 8.11$, $P = 0.04$), driven by a lower fixation discount rate in the DMF group. Post-hoc tests showed a trend toward a difference between the DMF and LF groups (Bonferroni corrected Mann-Whitney U test: $Z = 2.55$, $P = 0.07$, two-tailed), and controls ($Z = 2.40$, $P = 0.1$), and no other notable differences ($Z \leq 1.36$, $P \geq 0.9$). There were no significant group effects on drift rate constant (Fig 4b; Kruskal-Wallis test: $H_3 = 2.33$, $P = 0.5$) or threshold (Fig 4.4c; Kruskal-Wallis test: $H_3 = 1.51$, $P = 0.7$). There were also no differences between groups in the fit of the model (Supplementary Fig 4.6).

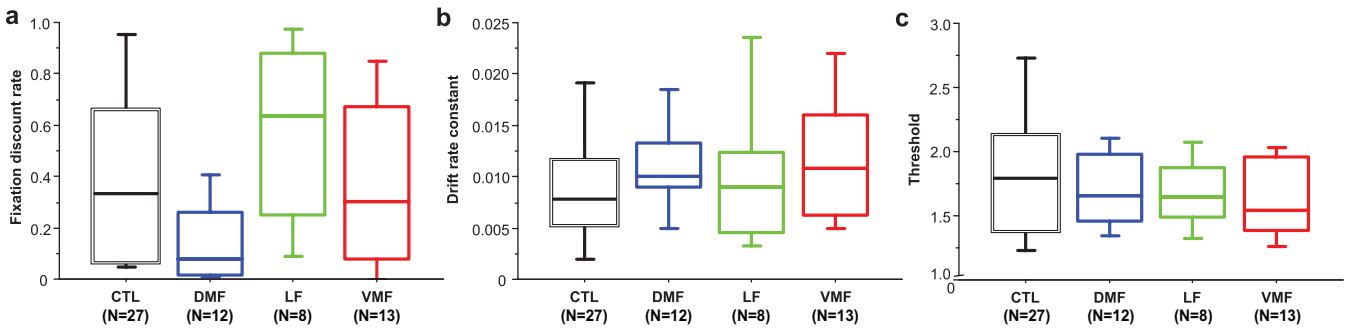


Figure 4.4. Parameter estimates from the attentional drift diffusion model (aDDM) in each group. (**a**) Fixation discount rate. (**b**) Drift rate constant. (**c**) Threshold parameter. Box plots show the 10th, 25th, 50th, 75th and 90th percentiles.

Rating consistency

Activity within VMF has been shown to scale with relative value in similar tasks studied using fMRI (Bartra et al., 2013; Lim et al., 2011; Rangel, 2013), but to our knowledge, there has been no direct test of whether any PFC region is necessary for consistently assigning a value rating to a stimulus. In a secondary analysis, we asked whether value ratings were more inconsistent in any frontal group by comparing the absolute difference and correlation of ratings of a separate set of artworks before and after the choice task.

There was a marginally significant effect of group on absolute value rating difference (between subjects Kruskal-Wallis test: $H_3 = 7.74$, $P = 0.05$) (Fig 4.5a). The DMF group was numerically more inconsistent, however post-hoc tests between groups did not find significant differences (Bonferroni corrected Mann-Whitney U tests: $Z \leq 2.22$, $P \geq 0.16$, two-tailed). When consistency was assessed by the correlation between test and retest ratings, there was no significant effect of group (between subjects Kruskal-Wallis test: $H_3 = 5.84$, $P = 0.1$) (Fig. 4.5b).

There was no significant effect of group on the absolute brightness rating difference

(Between subjects Kruskal-Wallis test: $H_3 = 3.14$, $P = 0.4$), nor any effect of group on the correlation between test and retest brightness ratings (Between subjects Kruskal-Wallis test: $H_3 = 5.72$, $P = 0.1$) (Fig. 4.5c-d).

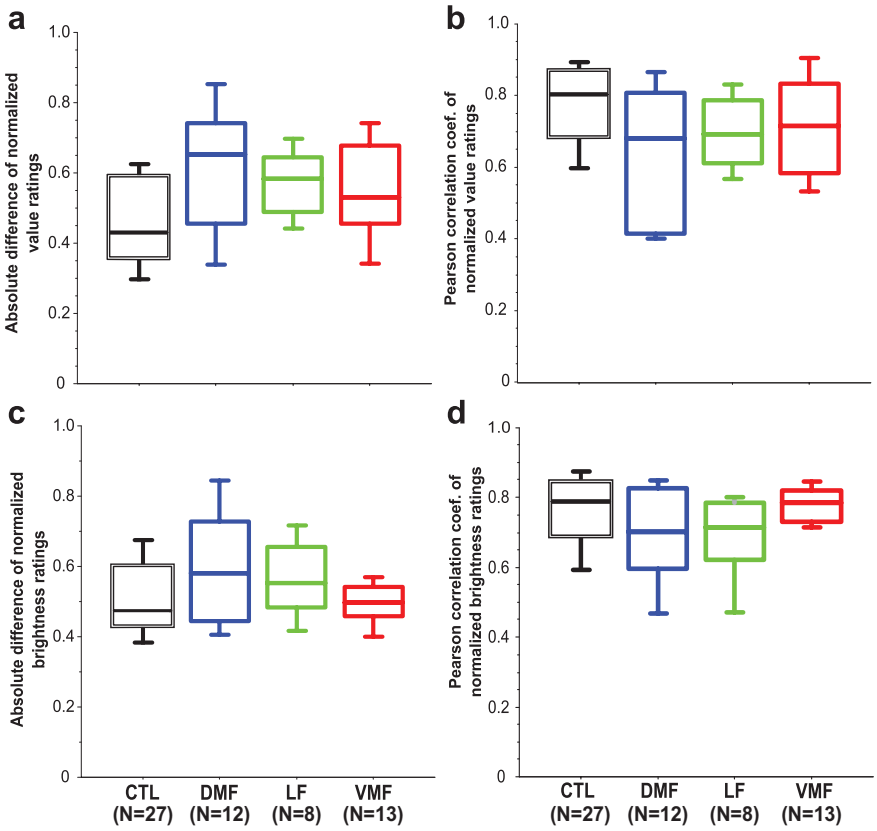


Figure 4.5. Measurements of consistency of value and brightness ratings of artworks in the test and retest phase of experiment by group. (**a**) Absolute difference of normalized value ratings. (**b**) Pearson correlation coefficients of normalized value ratings. (**c**) Absolute difference of normalized brightness ratings. (**d**) Pearson correlation coefficients of normalized brightness ratings. Box plots show the 10th, 25th, 50th, 75th and 90th percentiles.

We tested the relationship of value rating inconsistency with a simple index of fixation bias (Supplementary Fig 4.7) within control subjects. Simple regression analyses showed that fixation bias was correlated with age and education. We therefore included them in a multiple linear regression model as nuisance variables. While age and education were significant predictors of fixation bias, value rating consistency was not (Table 4.3).

Fixation bias residuals for all subjects were calculated based on the coefficients of this regression analysis. The increased fixation bias in the DMF group survived this correction, and was therefore not a result of inconsistent value ratings, or of age or education (Supplementary Fig. 4.8). Worse incidental memory performance in the PFC group as a whole showed a weak relationship with inconsistent value ratings, but not the degree of fixation bias (Supplementary Fig. 4.9).

Table 4.3. Multiple linear regression for normalized fixation bias in the control group.

Predictor	**Regression coefficient**	**Standard Error**	***P* value**
Intercept	-0.73	0.86	0.4
Education	-0.52	0.20	0.01
Age	0.04	0.01	0.01
Value rating inconsistency	-1.55	1.28	0.2

Model adjusted R^2=0.30. F-test against constant model: $F_{3,22} = 4.68$, $P = 0.01$. Education was treated as an ordinal variable (high school or less, undergraduate and graduate level).

Voxel-based lesion symptom mapping

While the region-of-interest approach provides evidence for a necessary role of DMF in mediating fixation bias, this method artificially limits regional specificity. Voxel-based lesion symptom mapping (VLSM) can overcome this limitation by testing the impact of damage on behavior at the voxel level (Bates et al., 2003; Rorden et al., 2007). VLSM is constrained by the degree of lesion overlap in the sample as a whole. In keeping with standard practice, we included voxels that were damaged in three or more patients in this analysis (Coulthard et al., 2008; Haramati et al., 2008; Tsuchida et al., 2010). Figure 4.6a shows the voxels where lesion-function relationships could be tested with this method in this study.

The residualized fixation bias index was entered into the VLSM analysis. The non-parametric Brunner-Munzel test (Brunner & Munzel, 2000) was applied at all voxels with

sufficient lesion overlap, and the threshold for statistical significance was determined using permutation testing to correct for multiple comparisons. Figure 4.6b shows voxels where damage was associated with an increased effect of fixation advantage on choice. Damage involving the left superior frontal gyrus was most strongly related to the behavioral effect. The strongest statistical effect ($P < 0.025$) was in a small cluster of voxels (MNI: -7, 20, 61) in the rostral pre-supplementary motor area (pre-SMA) (Picard & Strick, 1996; Tzourio-Mazoyer et al., 2002).

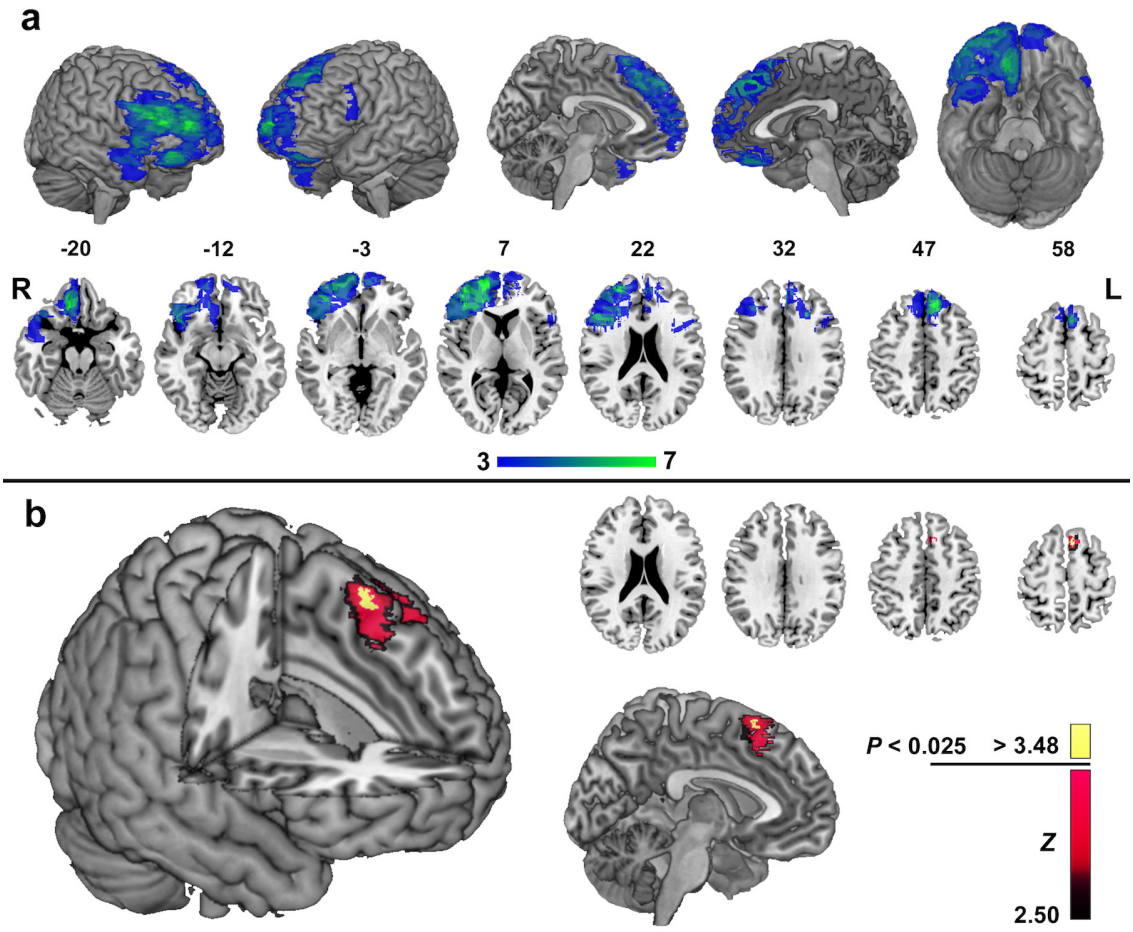


Figure 4.6. Voxel-based lesion symptom mapping (VLSM) for the effect of fixation advantage on choice. (**a**) Map showing the voxels where there was sufficient lesion overlap to detect an effect using VLSM methods, overlaid on the MNI brain in three-dimensional views, and in axial slices. Numbers above the axial slices correspond to z-coordinates in MNI space. The color scale indicates the number of patients with lesion overlap in any given voxel. R, Right L, Left. (**b**) VLSM statistical map computed for the effect of fixation advantage on choice overlaid on the MNI brain in a three-dimensional view (left), as well as a mid-sagittal view showing the medial wall of the left hemisphere (bottom) and on representative axial slices (top). The color scale indicates Brunner-Munzel *Z* scores. Voxels in yellow indicate where this effect was significant at $P < 0.025$, corrected with permutation tests.

Correlation of artwork ratings

Somewhat to our surprise, VMF patients made consistent value ratings, and choices consistent with these values. We explored whether the value judgments of these patients were similar to those of controls. The control subjects' average value ratings for each

artwork were significantly correlated with the average value ratings of all three PFC groups, but this relationship was weaker in the VMF group (Fig. 4.7a-c). In particular, the VMF group's average ratings were more variable for artworks the control group had rated below '0.' In contrast, ratings of artwork brightness were highly correlated between controls and all PFC groups (Fig. 4.7d-f).

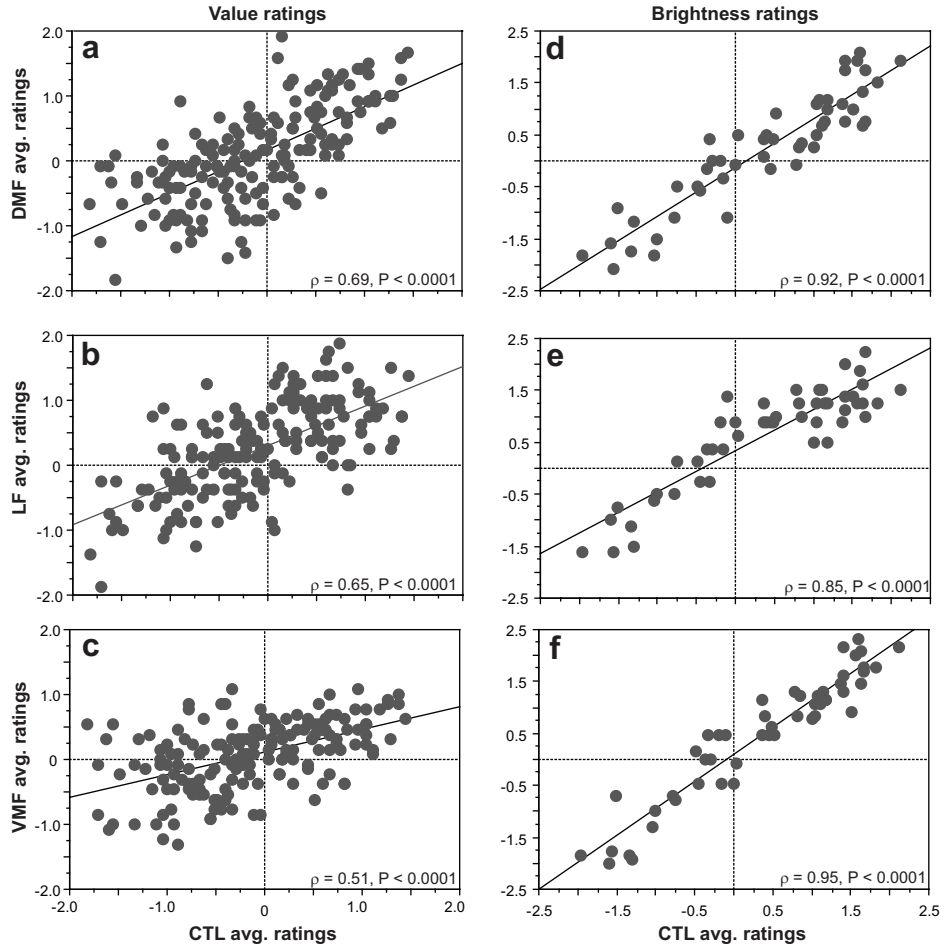


Figure 4.7. Scatterplots of average ratings of all artworks for each group in the initial value rating task (175 artworks) and brightness rating task (50 artworks). Average artwork value ratings of DMF, LF and VMF groups are plotted against control subjects (CTL) in panels **a-c**, respectively. Average artwork brightness ratings for DMF, LF and VMF average are plotted against the control group in panels **d-f**, respectively. Average only includes subjects' initial ratings (i.e. no data from the retest phase). Spearman correlation coefficient and associated *P* values are shown in the bottom right-hand corner of each panel.

Discussion

Several recent studies have found that visual fixations during deliberation can influence value-based decisions (Armel et al., 2008; Krajbich et al., 2010; Krajbich et al., 2012; Krajbich & Rangel, 2011; Shimojo et al., 2003; Towal et al., 2013), an observation that opens a novel window on the dynamic construction of value during choices. Here, we applied this experimental approach to test whether focal PFC damage affects this aspect of value updating. The choices of all groups were influenced by both their *a priori* value assessment of the options, and by fixations during the choice process. Damage to DMF, and not other PFC regions, was associated with a significant increase in the influence of fixations on choice.

Existing efforts to relate fixation-driven updating to neural mechanisms have focused on value-related signals in ventromedial PFC (Lim et al., 2011). That account would predict a reduced influence of fixations on choice after VMF damage, which we did not observe. Indeed, the VMF group was intact in nearly all aspects of this task, a striking finding given the putative central role of this region in current models of value-based decision-making (Kable & Glimcher, 2009; Padoa-Schioppa & Assad, 2006; Rangel & Clithero, 2013). Previous work from our group has found that VMF damage disrupts preference transitivity (Fellows & Farah, 2007; Henri-Bhargava et al., 2012). This finding has been taken as evidence that this region is required for consistent comparisons, but could support other models of the role of this region, such as a role in constructing a superordinate hierarchy of option values (Stalnaker et al., 2015). Here, for the first time, we directly tested the stability of value ratings for individual options, and found that VMF damaged patients provided consistent ratings over the course of the experiment and made choices that were more

consistent with these ratings (in economic terms, more rational) than controls. These findings align with studies in monkeys demonstrating intact preference based choice after orbitofrontal lesions (Izquierdo et al., 2004), and present a challenge to simple views of ventromedial PFC as universally necessary for assessing and comparing the economic values of options.

The intact, even supra-normal, behavior of VMF damaged patients might reflect differences in the information used to make value ratings. As with all ecologically valid stimuli, artwork can be assessed on a range of attributes (Chatterjee, Widick, Sternscein, Smith, & Bromberger, 2010), presumably integrated to produce a single subjective value estimate that has been a focus of much neuroeconomics work to date. Imaging studies suggest a role for VMF in the integration of value information from multiple sources (Lim et al., 2013; Philiastides et al., 2010). Here, value ratings of the VMF group agreed less with those of controls, suggesting these assessments might be based on different attributes, or different attribute weightings. In recent work with social stimuli, we found that VMF damage disrupts the integration of attributes: these patients used simpler information to inform their choices than did controls (Xia, Stolle, Gidengil, & Fellows, 2015). Thus, VMF damage may affect the information used by patients to assign value to items, rather than the ability to report or compare those values once assigned. Indeed, those with VMF damage may simplify the value construction problem as a compensatory strategy (Fellows, 2006). Addressing this possibility fully will require approaches that impose better experimental control over the 'value construction' process that work in this field to date has largely left unconstrained.

Damage to DMF, and not other PFC regions, was associated with an increase in the

influence of fixations on choice. An exploratory model-based analysis of this dataset suggested that the increased influence of fixations in the DMF group could be accounted for by discounting the value of the unfixated option during the decision process. While the results of this post-hoc model-based analysis should be considered preliminary, they complement the main GEE analyses that took full advantage of this dataset. , That primary analysis showed a robust increase in the influence of fixations in the DMF group and decreased sensitivity to the value rating difference of the fixation advantaged and alternative options, as would be predicted by a decrease in the fixation discount rate in the model (Krajbich et al., 2010). DMF may thus be necessary for maintaining the value of unattended options. This result aligns with findings from foraging tasks where activity within DMF tracked the value of departing from a default option and exploring alternatives (Kolling et al., 2012; Quilodran et al., 2008). The fMRI data supporting this view have recently been challenged, with the alternative hypothesis that this signal reflects choice difficulty, or conflict (Shenhav et al., 2014). The predictions of the latter model in terms of lesion effects in this task are not entirely clear, but we note that our prior work has failed to find consistent effects of DMF lesions on behavioral indices of conflict monitoring in a variety of tasks (Fellows & Farah, 2005b). Further, here we found that the performance of DMF patients was sensitive to choice difficulty, as indexed by RT and fixation data.

These findings agree with other work placing DMF at a critical juncture linking value comparison and action selection (Camille, Tsuchida, et al., 2011; Hare, Schultz, Camerer, O'Doherty, & Rangel, 2011; Rudebeck, Behrens, et al., 2008). Voxel-based analysis in this large PFC sample revealed that increased fixation bias was driven by damage within the pre-SMA. Damage to the pre-SMA/SMA has been associated with failure of goal-directed

control over externally triggered responses (Nachev, Kennard, et al., 2008; Parton et al., 2007) and can cause utilization behavior, a clinical phenomenon in which behavior is excessively influenced by environmental cues (see Iaccarino, Chieffi, and Iavarone (2014) for a recent review). The increased fixation bias associated with pre-SMA damage in the current study could be interpreted as exaggerated environmental control over decision-making, arguing for a specific role of pre-SMA in mediating the influence of attention during the choice process.

Human lesion studies have intrinsic limitations that should be kept in mind in interpreting these results. Sample size is limited by practical considerations, particularly when the behavior is measured in detail, as here. The power to detect effects also varies with the extent of lesion overlap and the covariance of damage within individual lesions. While the sample studied here is relatively large by the standards of such work, and the expected effect size in lesion studies is moderate-to-large, power remains a perennial concern in interpreting both the null and positive findings (Fellows, 2012). The overlap map (Fig 4.6a) is a guide to those PFC regions we are best placed to test in this sample. It should be noted that these lesions also affect underlying white matter to varying degree. Although consistent effects of white matter damage should be revealed in the voxel-based analysis, it is difficult to fully distinguish effects of cortical damage from effects on underlying fibers of passage with potential impact on brain function at a distance from the site of injury. The findings thus need to be considered in the context of evidence from multiple techniques.

Finally, we note that the design of the experiment required that initial ratings meet certain criteria. Two VMF subjects and one healthy control were excluded from the

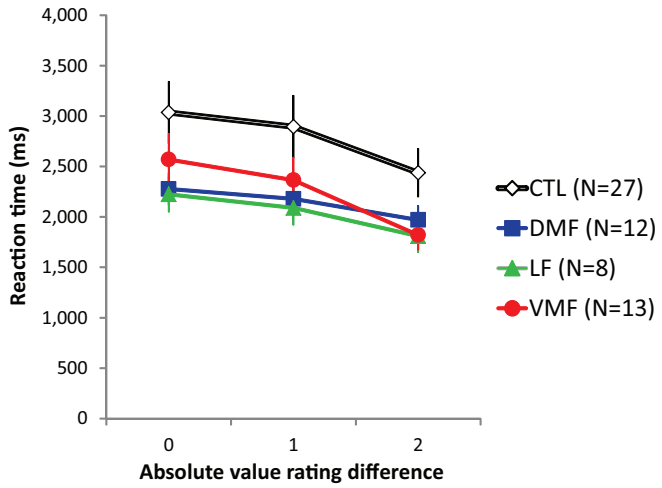
experiment for failing to meet these criteria, biasing the VMF sample towards those able to make value ratings along the specified range.

These findings provide convergent support for some, but not all, elements of current neurobiological models of the influence of attention on value-based choice. We clearly show that intact VMF is not required for fixation-based value updating, challenging a simple view of VMF as a general, dynamic 'value-meter'. In contrast, DMF makes a necessary contribution to this process, allowing information about the value of the currently unattended option to influence choice.

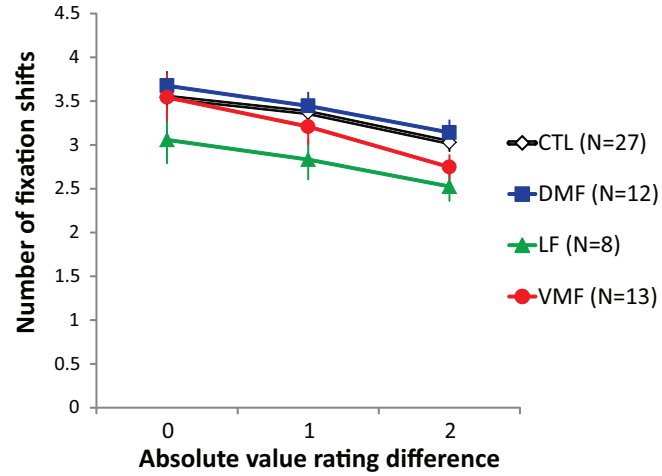
Acknowledgements

We thank Arlene Berg and Christine Déry for help with subject recruitment, and Chenshuo Jin, Nancy Mayo, Susan Scott and Stanley Hum for help with data analysis. We would like to particularly thank Antonio Rangel for his generous help and advice regarding the analysis. Daniel Guitton and Kate Rath-Wilson provided helpful comments on the manuscript. This work was supported by an operating grant from CIHR (MOP 97821), a Fonds de Recherche en Santé du Québec Chercheur-Boursier award to LKF, and a Desjardins Outstanding Student Award to ARV. We would also like to thank the many McGill-affiliated physicians who refer patients to this research program, and the patients and healthy volunteers for their participation.

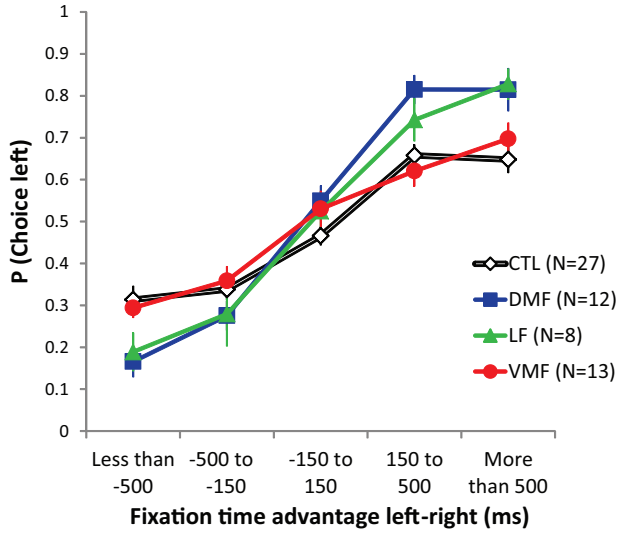
Supplementary material



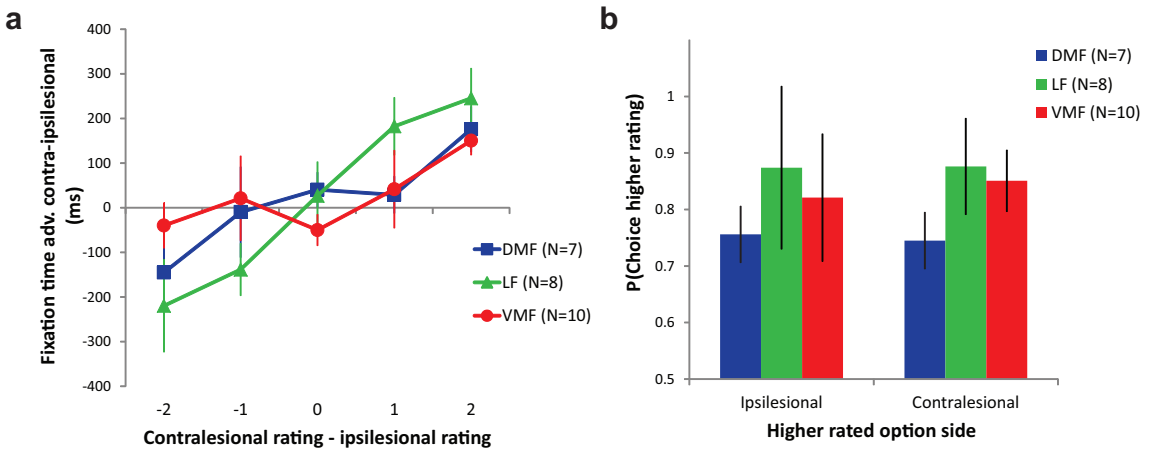
Supplementary Figure 4.1. Reactions time as a function of the absolute value rating difference of left and right options with outliers (RT greater than 2 standard deviations from subject's mean) removed. Patients and controls responded faster as the absolute value rating difference increased (Mixed measures ANOVA: $F_{2,112} = 27.22$, $P < 0.0001$). There was no significant main effect of group ($F_{3,56} = 1.82$, $P = 0.1$), or interaction between group and value difference ($F_{2,112} = 1.01$ $P = 0.4$). Error bars represent the SEM.



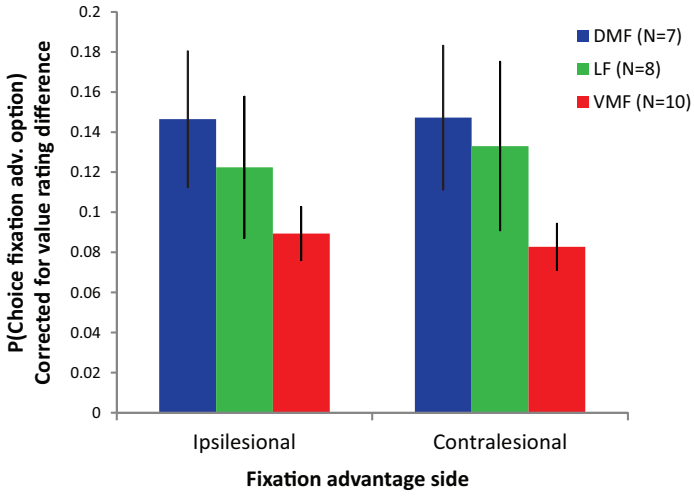
Supplementary Figure 4.2. Average number of fixations as a function of the absolute value difference between options. There was a significant main effect of absolute value difference, with the number of fixations decreasing as the absolute value difference between options increased (Mixed measures ANOVA: $F_{2,112} = 36.19$, $P < 0.0001$). There was no significant main effect of group on the number of fixation shifts ($F_{3,56} = 1.92$, $P = 0.1$), or interaction between value difference and group ($F_{6,112} = 0.54$, $P = 0.7$).



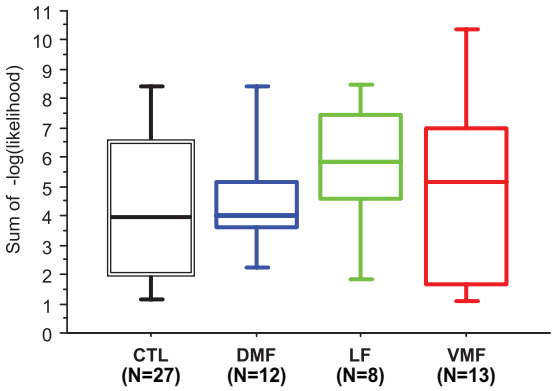
Supplementary Figure 4.3. Effects of raw fixation advantage on choice of the left option. Using this measure in the GEE, we found that the best model included interactions of group with value rating difference and fixation advantage, but not saliency. There were main effects of value rating difference (OR: 2.65, CI: 2.30-3.05, $P < 0.0001$), fixation advantage (OR: 1.52, CI: 1.39-1.67, $P < 0.0001$) and saliency (OR: 1.22, CI: 1.08-1.38, $P = 0.001$). The DMF group was marginally more likely than controls to choose the left option over the right option overall (OR: 1.29, CI: 1.02-1.65, $P = 0.03$). We found no differences in the effect of value ratings on choices in DMF (OR: 0.86, CI: 0.70-1.06, $P = 0.2$), LF (OR: 1.38, CI: 0.82-2.33, $P = 0.2$) or VMF (OR: 1.22, CI: 0.99-1.52, $P = 0.07$) groups compared to controls. The effect of fixation advantage was greater in the DMF group compared to controls (OR: 1.57, CI: 1.21-2.05, $P = 0.0008$). In contrast, the influence of fixation advantage on choice in the LF group (OR: 1.45, CI: 0.95-2.20, $P = 0.08$) and the VMF group (OR: 1.05, CI: 0.91-1.21, $P = 0.5$) was not significantly different from controls. Error bars represent the SEM.



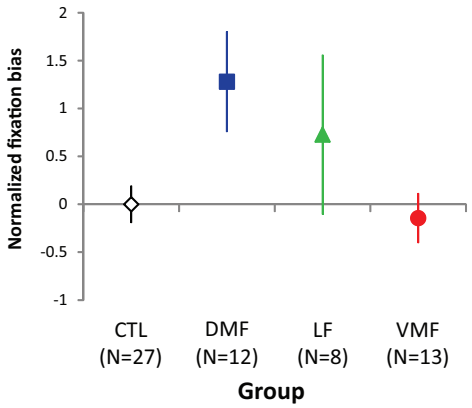
Supplementary Figure 4.4. Contra- and ipsilesional effects of value ratings on fixation advantage and choices in 25 patients with unilateral damage. (**a**) Fixation time advantage to contralesional-ipsilesional options as a function of the rating difference of these options. There was a significant main effect of rating difference on fixation advantage (Mixed measures ANOVA: $F_{4,88} = 11.23$, $P < 0.0001$). However there was no significant main effect of group ($F_{2,22} = 0.01$, $P = 0.9$), or interaction between group and rating difference ($F_{8,88} = 1.75$, $P = 0.1$). (**b**) Probability of choosing higher rated option on contra- or ipsilesional side. There was a significant main effect of group (Mixed measures ANOVA: $F_{2,22} = 4.00$, $P = 0.03$), with the LF group choosing the higher rated option significantly more often than DMF group (Bonferroni corrected t-tests, collapsed across side: $P = 0.009$, two-tailed). Critically, there was no significant effect of side ($F_{1,22} = 0.06$, $P = 0.8$), or interaction between side and group ($F_{2,22} = 0.18$, $P = 0.8$). Error bars represent the SEM.



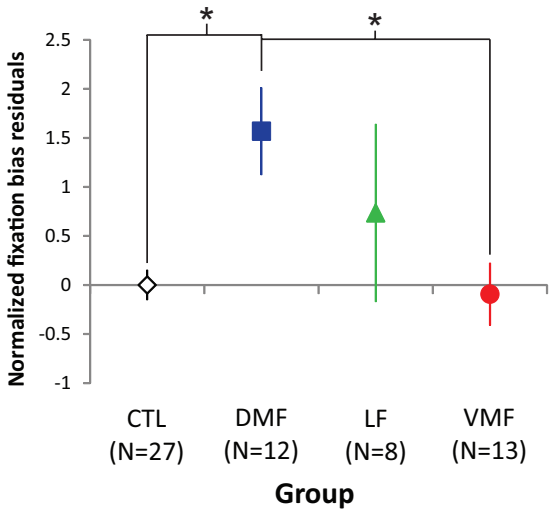
Supplementary Figure 4.5. Probability of choosing the fixation-advantaged option when it appeared on the contra- or ipsilesional side, corrected for value difference, in 25 patients with unilateral damage. Critically, there was no effect of side ($F_{1,22}$ = 0.12, P = 0.7), or interaction between side and group on the probability of choosing the fixation-advantaged option ($F_{2,22}$ = 1.26, P = 0.3). There was also no main effect of group ($F_{2,22}$ = 1.24, P = 0.3) in this sample of patients. However, the pattern of results was not different from complete patient sample. Error bars represent the SEM.



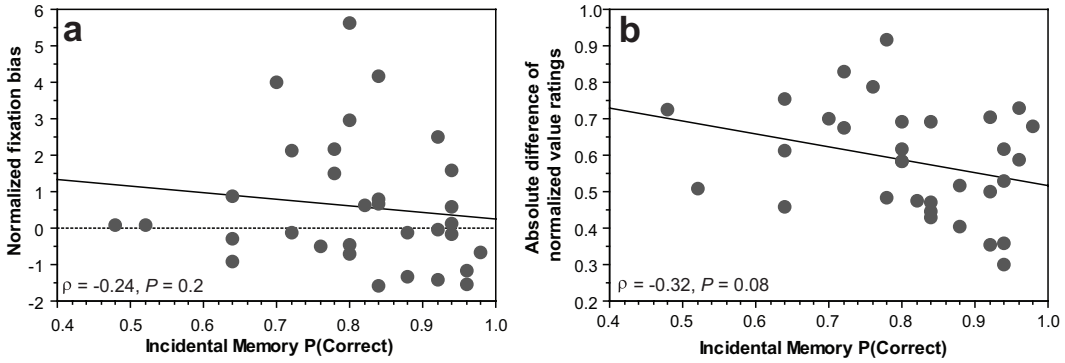
Supplementary Figure 4.6. Model fitness in each group, calculated as the sum of the negative log likelihood of *P*-values from Kolmogorov-Smirnov tests in the three value difference conditions (0, 1, 2). There was no effect of group status on this measure (Kruskal-Wallis test: H_3 = 1.53, P = 0.7). Box plots show the 10th, 25th, 50th, 75th and 90th percentiles.



Supplementary Figure 4.7. Index of fixation bias corrected for value difference and normalized to controls' scores. There was a significant main effect of group on fixation bias (Between-subjects ANOVA: $F_{3,56} = 3.01$, $P = 0.04$). Post-hoc tests found that the fixation time bias of the DMF group approached a significant difference from the control group ($P = 0.07$, corrected, two-tailed) and VMF group (Bonferroni corrected t-test: $P = 0.09$, two-tailed). All other post-hoc comparisons between groups were not close to significant (P's ≥ 0.9 corrected). Error bars represent the SEM.



Supplementary Figure 4.8. Normalized fixation bias residuals after subtracting fixation bias predicted by age, education and value rating difference. There was a significant main effect of group on residualized fixation time bias (Between-subjects ANOVA: $F_{3,56} = 4.45$, $P = 0.007$). Post-hoc tests found that the fixation bias of the DMF group was significantly greater than the control group (Bonferroni corrected t-test: $P = 0.01$, two-tailed) and VMF group ($P = 0.02$). There were no other significant post-hoc differences after correction for multiple comparisons (P's ≥ 0.9, corrected). Error bars represent the SEM. * $P < 0.05$, Bonferroni corrected t-test, two-tailed.



Supplementary Figure 4.9. Scatterplots showing relationship of incidental memory with (**a**) normalized fixation bias, and (**b**) value rating inconsistency across all patients where incidental memory scores were available (N=32). Spearman correlation coefficient and associated *P* values are shown in the bottom left-hand corner of each panel.

Supplementary Table 4.1. Quasi-Akaike Information Criteria (QIC) and associated Akaike weights for GEE models.

Model	**QIC**	**Akaike Weights**
Choice of left option		
Simple (no interactions)	6139.01	2.17e-8
Group X Rating difference	6132.37	6.02e-7
Group X Fixation advantage	6115.38	2.95e-3
Group X Saliency	6142.55	3.71e-9
Group X Rating difference Group X Fixation advantage	6104.20*	0.79
Group X Rating difference Group X Saliency	6135.23	1.44e-7
Group X Fixation advantage Group X Saliency	6119.20	4.37e-4
Group X Rating difference Group X Fixation advantage Group X Saliency	6106.87	0.21
Choice of fixation-advantaged option		
Simple model	6095.37	0.02
Group X Rating difference	6087.42*	0.98

* Best fit model based on QIC

Chapter 5: Conclusion

Whether foraging on foot in the bush or negotiating the jungle of online retail by cursor, we frequently navigate dynamic decision environments replete with potential actions and sensory cues signaling uncertain and unstable outcomes. Moreover these options and their indicators differ dramatically in their relevance, predictive value and relative salience. That we can make any adaptive choices in such a crowded, noisy sensory environment is testimony to the sophistication of our decision circuitry. Understanding how such decisions are made requires examining how selective attention enables the filtering of these inputs to focus on cues that are predictive of future outcomes, in turn allowing the decision-maker to gather relevant evidence about decision options to inform choice behavior.

In this doctoral thesis, I investigated the involvement of the frontal lobes in attention during value-based decision-making and associative learning. The three studies detailed here examined how frontal lobe damage affected the interaction of selective attention with reward leaning and value-based choice. This work uncovered unique contributions of frontal sub-regions to guiding attention to reward-predictive stimuli, attentional filtering of relevant and irrelevant stimulus dimensions during learning, and attentional bias during value-based choice. This final chapter briefly summarizes the key findings, and presents a general discussion of the significance of this work as well as suggestions for future directions.

The first study examined the effects of frontal lobe damage in a visual search task where the task-irrelevant color of a target item was incidentally predictive of rewards. Previous work had found that similar manipulations yield a trial-by-trial priming effect,

where distractors exert a larger influence on attention when they appear in a color that is associated with large rewards compared to colors associated with small rewards (Hickey et al., 2010a; Kristjansson et al., 2010). Here, this priming effect was replicated in healthy control subjects and patients with LF and DMF damage, however it was absent in patients with VMF damage, even after extensive exposure to these reward associations over the period of the experiment. The results of this study indicate that VMF is critical for directing attention to reward predictive stimulus features. Attention to reward-predictive stimuli is thought to be important for modulating the extent to which new information is extracted from experience with future feedback (Kruschke, 2003; Mackintosh, 1975). By guiding attention to reward-predictive stimuli, VMF might therefore modulate the learning rate for these stimulus options, potentially providing a mechanistic explanation for VMF-associated deficits in stimulus-value learning tasks observed in past work (Butter, 1968; Dias et al., 1996a; Fellows & Farah, 2003; B. Jones & Mishkin, 1972; Tsuchida et al., 2010).

The second study investigated the effects of frontal lobe damage on learning in a task where stimulus options varied along multiple dimensions, only one of which was predictive of whether options were rewarding or not. This task tested the ability of subjects to appropriately attribute feedback to the less salient, but relevant stimulus dimension, while ignoring the more salient, irrelevant stimulus dimensions. Subjects with left LF frontal damage were profoundly impaired in this task, crediting rewards to the side (or action) chosen in the last trial, even though this dimension had no predictive value. In contrast, VMF damaged subjects did not attribute rewards to the irrelevant features more than healthy controls, but were impaired in learning about the relevant dimension. These different patterns of impairment suggest that these sub-regions make unique contributions

to performance in this task that are in line with other deficits observed in these patients in past work. These findings suggest that the contributions of lateral PFC to selective attention and cognitive control also have ramifications for stimulus-value learning, namely in the selection of relevant, reward-predictive features for appropriate feedback attribution. In contrast, VMF damaged subjects were not more distracted by these irrelevant dimensions, but apparently failed to highlight the relevant, predictive dimension during reward attribution.

The third study tested the contributions of these frontal sub-regions to value-based decisions between naturalistic stimuli, and the influence of attention on those choices. Subjects provided value ratings for a large set of artworks and then chose between these items in pairs while their eye movements were tracked, as in past work (Krajbich et al., 2010; Krajbich & Rangel, 2011). In contrast to expectations from past work (Lim et al., 2011), the choices of subjects with damage to DMF, and not VMF, were influenced by fixations more than controls. DMF damaged patients appeared to discount the value of the unfixated option such that their choices were driven by the value of the option that was preferentially fixated rather than the *a priori* relative value of the two options. Notably, all patient and control subjects were also able to make internally consistent value ratings over the experimental session, and choices that were consistent with these ratings. These findings also demonstrate that VMF is not necessary for dynamically updating decision values with information extracted from options through visual fixation, or for making judgments or choices based on subjective value, at least in some generic sense.

VMF damage was associated with behavioral patterns in visual search and associative learning that are consistent with the notion that this region is critical for biasing

attention based on predictive value. Failure to use feedback history to allocate attention to relevant, reward-predictive stimulus features likely has downstream consequences for learning and decision-making. In particular, by allocating attention to reward-predictive stimuli, VMF might facilitate learning by focusing attention on reward predictive features (Mackintosh, 1975), or orienting to previously neutral stimuli based on their acquired incentive salience (Robinson & Berridge, 1993), both of which may be critical for optimally harvesting rewards from the environment.

Notably, VMF damaged subjects were sensitive to the apparent information value within stimulus dimensions based on local correlations with reward, yet failed to stick with features within the ultimately predictive dimension. This finding suggests that VMF may not be necessary for shifting attention to stimulus dimensions based on these short-term correlations with reward, but may instead be involved in prioritizing stimulus dimensions with more stable predictive value. OFC damage in monkeys and humans does not affect the ability to shift attention between stimulus dimensions (Dias et al., 1996a; Glascher et al., 2012; Milner, 1963), in line with this result. This impairment in focusing attention on the reward-predictive dimension is likely not just the result of a failure to heed task instructions, as the study in Chapter Two demonstrates that VMF damage affects the ability to direct attention to reward predictive features even when stimulus-reward learning was not emphasized by task instructions. Thus, these results argue that attentional allocation based on local reward associations is preserved in these patients, but the ability to form a more stable attentional set for motivationally relevant stimuli may be impaired.

In the study described in Chapter Two, measurement of the effects of reward priming on attention and the implicit exposure to reward-feature associations took place in

the same task. As a result, it is difficult to know whether the lack of reward priming in these patients stemmed from a failure to learn these associations, or inability to allocate attention to rewarding stimuli. These processes are fundamentally linked in most settings, as the allocation of attention to features boosts future learning about the relationship of these features with feedback (Kruschke, 2003; Mackintosh, 1975). However, these processes could be experimentally uncoupled by testing attentional allocation to a cue that subjects had learned to associate with reward through extensive prior training (similar to Anderson et al. (2011b)). We expect that VMF damaged subjects would attend to this cue as well as healthy controls, as the reward value would already have been learned, and VMF damage does not affect deterministic conditional learning (Dias et al., 1996b; Fellows & Farah, 2003). This first study was designed to instead better match probabilistic settings where subjects with VMF damage are known to have learning impairments (Tsuchida et al., 2010; Wheeler & Fellows, 2008), and thus was more relevant to understanding the mechanistic underpinnings of these deficits.

The results of Chapter Four also have relevance in addressing the necessity of VMF in guiding attention to rewarding stimuli more generally. VMF damaged subjects preferentially spent more time fixating artworks that they had earlier assigned a higher value rating, arguing that this region is not necessary for directing attention to stimuli with greater subjective reward value *per se*. However, the different operationalizations and timescale of attention in these two tasks (i.e. fast reaction time effects versus longer fixation time differences) make it difficult to directly compare these effects. The first two studies examined attentional effects on choices and target discrimination times that were in the order of less than a second. Moreover, stimuli were masked in these studies, forcing

subjects to rapidly engage selective attention, whether based on relevance for goals or reward-value. These effects may therefore depend on the rapid involvement of PFC in directing attention within posterior sensorimotor areas within a few hundred milliseconds of stimulus presentation (Buschman & Miller, 2007; Voytek & Knight, 2010). While the time course of interaction between OFC and ventral visual areas has received less attention compared to lateral PFC, magnetoencephalography data in humans suggests this interaction may occur in a similar timeframe (Bar et al., 2006). In contrast, eye-movements in the third study took place over the course of seconds, a time course that might have allowed for alternative sources of subjective value information to influence attention. Furthermore, this task used naturalistic stimuli with endogenous reward value, which VMF patients appeared to be sensitive to, as evidenced by their reaction times and choices. An attentional blink task using distractors with inherent or learned value associations could determine if the effects of VMF damage on attention are dissociable for these two types of stimuli in the same experimental context and on a similar rapid time course.

These results also raise questions regarding the mechanism by which VMF influences attention. The polymodal bidirectional connections of this region to sensory areas, as well at indirect mediatory connections with subcortical structures, leave open many possible channels (Price, 2007). For example, connections between posterior OFC and inhibitory centers in the amygdala and thalamus could help determine the influence of motivational signals on attentional selection (Barbas et al., 2011). Future work could systematically examine the timing of these attentional effects and the underlying circuitry that enables VMF to interact with posterior sensory regions. We are currently carrying out a follow-up experiment, testing patients with VMF damage and healthy controls in the

same visual search task described in Chapter Two while recording brain activity with magnetoencephalography. This study might help determine how VMF damage affects attention, and better establish how this region contributes to reward-based attention modulation in healthy subjects.

While the first two studies in this thesis focused on the role of VMF in reward learning and attention, it is not clear from this work alone if this role of VMF is specific for reward-guided behavior or is more generally important in focusing attention on features of the environment that are simply predictive *per se*. In line with this hypothesis, other lesion work has implicated this region in the Weather Prediction Task (WPT), where outcomes with no inherent reward value (i.e. sunny or rainy days) have to be predicted on the basis of visual cues (Chase et al., 2008). A recent model of OFC function has suggested that this region represents task contingencies in a 'cognitive map' that enables representation of the 'hidden' variables within a task (Wilson et al., 2014). The predictions derived from this internal model are not necessarily related to reward value, but could be any outcome that has be inferred from past experience. Within the context of this hypothesis, the role of this region in shifting attention to predictive features might be a consequence of this internal representation of inferred task contingencies, built up based on a history of feedback. Recent electrophysiological work in rats suggests that the population activity of OFC neurons encodes task dimensions within a framework of expected reward, in line with this cognitive map hypothesis (Farovik et al., 2015). Failure to form such a representation of the relationship between stimulus dimensions and reward in the second study could similarly underlie the inability of VMF damaged subjects to give attentional priority to the relevant dimension.

The results of this thesis also speak to distinct, but critical contributions of other frontal sub-regions during associative learning. The performance of VMF damaged subjects was unaffected in other aspects of these tasks requiring top-down control of selective attention. In contrast, subjects with left LF damage had difficulty ignoring the salient, irrelevant dimensions in the multidimensional reversal learning task. These findings echo previous work that has found dissociable impairments of selective attention related to LF, but not VMF, damage across species (Dias et al., 1996a; Glascher et al., 2012; Tsuchida & Fellows, 2013). The results of the second study indicate that these deficits severely affect the ability of left LF damaged patients to appropriately attribute feedback to a relevant stimulus dimension in face of salient distractors. The lateralization of this effect might be related to the symbolic, letter-like quality of the stimuli used in that study, i.e. be a manifestation of content-specialized cognitive control (Thompson-Schill et al., 2005). Testing this hypothesis would require asking left and right LF damaged subjects to complete a redesigned version of this task using a different relevant dimension, or different shapes.

The lateralization of the deficits in LF patients may also relate to a specialized role for the left hemisphere in hypothesis-based action (Wolford, Miller, & Gazzaniga, 2000), focusing attention on stimulus dimensions that are in line with a current theory about the task environment, in this case derived from task instructions. Notably, in addition to preferentially attributing rewards to features within irrelevant stimulus dimensions, left LF damaged subjects were also more likely to switch these irrelevant dimensions, based on their apparent predictive value in recent trials. This finding argues that this region helps select which stimulus dimensions are considered as potentially predictive of reward. While

this result is perhaps surprising given that LF damage impairs attentional shifting in other contexts (Buchsbaum, Greer, Chang, & Berman, 2005; Dias et al., 1996a; Tsuchida & Fellows, 2013). However, these effects of LF damage may be linked by a common failure in flexibly deploying an attentional template based on current expectations about the relevance of stimulus dimensions. Without top-down control through such a template, attention may instead be captured by visual salience or local correlations between stimulus features and reward.

LF and VMF might have complimentary roles in multidimensional learning. In their biased competition model of decision-making, Cisek and Kalaska (2010) suggest that stimulus-value information represented in OFC influences sensorimotor representations indirectly through VLPFC. However, the first study in this thesis demonstrates that VLPFC is not necessary for attentional biases to reward-predictive stimuli. The results here indicate that LF filters representations of the environment to prefer features emphasized by task instructions or an internal hypothesis, as past influential models of PFC function have argued (Miller & Cohen, 2001), but is not necessary for selecting features based on reward value. However, the interaction between these regions may have other critical functions. Recent functional imaging work also suggests that connections between lateral PFC and vmPFC are critical for the top-down modulation of decision-making. Coupling between vmPFC and VLPFC activity is related to the fidelity of value-based choices in the face of distractor items (Chau et al., 2014). Relatedly, lateral PFC has been suggested to enable self-control over food choice by modulating the weights of food attributes reflected in vmPFC value signals, potentially through attentional mechanisms (Hare, Camerer, & Rangel, 2009; Hare, Malmaud, et al., 2011). Thus, rather than acting as a waystation for

VMF-derived value signals, LF may help bias decisions by influencing value processing in VMF.

Together, these data argue that LF may shape the decision space by selecting features or options based on relevance to current goals, while VMF helps select features based on reward history. Importantly, filtering out these stimulus dimensions may be maladaptive when the predictive value of different stimulus dimensions is in flux and a current hypothesis about the environment is no longer correct (Chrysikou et al., 2014). This prediction could be further examined by testing VMF and LF damaged patients in a reward learning task where misleading instructions place reward value and an instructed hypothesis about behavioral relevance in opposition. In such a case, LF damaged subjects might paradoxically outperform control subjects by failing to direct attention according to instructions. In contrast, VMF damaged subjects might be hindered by following instructions, and further impaired due to an inability to take advantage of reward history to modify the allocation of attention.

Left LF damage may also have affected the integrity of learned stimulus-reward relationships in a stream of recent experience. An abundance of work indicates that lateral PFC damage, particularly in the left hemisphere, is critical for the integrity of memory in the face of interference (Chao & Knight, 1998; Shimamura et al., 1995; Tsuchida & Fellows, 2009), and may be related to impairment in monitoring a sequence of internally selected responses. This latter ability is disrupted after damage to mid-DLPFC in humans and monkeys (Petrides, 1991; Petrides & Milner, 1982). In a similar vein, previous work has shown that damage to lateral OFC or VLPFC (PPA 47/12) affects the fidelity of learning about the relationship between feedback and choice history in monkeys in a reward

learning task with three stimulus options (Noonan et al., 2010). While left LF damaged subjects were sensitive to the history of feedback for irrelevant features, these patients may have had difficulty maintaining the value of features within the less salient relevant dimension in working memory, or monitoring the history of feedback for past choices in this dimension. A more focused study of the effects of damage in patients with restricted lesions to lateral OFC, VLPFC and DLPFC might help elucidate the contributions of these regions in maintaining the fidelity of choice and reward history.

The results of this work also pose fundamental questions regarding the neurobiological basis of value-based choice. VMF damaged patients gave internally consistent value ratings and made choices consistent with these ratings. These findings challenge the notion that VMF is critical in any generic judgment or decision based on reward value, as suggested by the pervasive finding of hemodynamic subjective value signals in this region during various decision tasks (Bartra et al., 2013; Clithero & Rangel, 2014). This result joins other accumulating evidence from animal models demonstrating that OFC is not generically necessary for choices based on subjective value (Izquierdo et al., 2004; J. L. Jones et al., 2012a; Rudebeck & Murray, 2011a), and does not necessarily code a common subjective value signal across all experimental settings (Blanchard, Hayden, & Bromberg-Martin, 2015; Hosokawa et al., 2013). Importantly, signals for subjective value or value comparison are not unique to vmPFC, and may be distributed throughout the reward circuitry (Bartra et al., 2013; Kennerley et al., 2011; Strait et al., 2015). Imaging studies in particular have frequently found that the ventral striatum and posterior cingulate cortex are co-activated with vmPFC during subjective value coding (Bartra et al., 2013; Clithero & Rangel, 2014), though much less is known about the necessary

contributions of these regions to decision-making or subjective value judgment in humans. Future work will be needed to determine how damage to these regions affects the evaluation of subjective value and decision-making.

While VMF-damaged patients were able to make internally consistent value ratings for artworks, these value judgments may not have been constructed the same way as in other groups. It is generally assumed that value information from option attributes is integrated during judgment of complex, multi-faceted stimuli, like food or artwork (Rangel & Clithero, 2013). Imaging work has implicated vmPFC in the integration of value information (Kahnt, Heinzle, Park, & Haynes, 2011; Philiastides et al., 2010), however the critical role of this region has not been well characterized. A recent study from our group argues that this process might be simplified, or rely more on perceptual features than conceptual information, in patients with lateral OFC damage (Xia et al., 2015). We are currently carrying out a follow-up analysis to the study in Chapter Four, asking whether VMF damage affected the weighing of artwork attributes. By testing how subjects' value ratings are related to artwork attributes (e.g. abstractness, color saturation) defined in the aesthetics literature (Chatterjee et al., 2010), we will determine if these patients differed in weighting these attributes during their value judgments.

Devoting attentional priority to certain stimulus attributes over others may affect the weighting of these attributes during value judgment (Payne et al., 1993). Future work is needed to test if VMF damage systematically affects attention to option attributes, or impairs the ability to set appropriate weights for attributes that have greater motivational relevance for the decision at hand. Such a line of investigation may provide a critical link between VMF-related learning deficits, and reduced attention to reward-predictive

features, as described in the first two studies, and the putative role of this region in forming value judgments, or signaling expected value more generally.

This thesis work also showed that VMF damage did not affect the influence of fixations on decision-making. The sole imaging experiment examining the effects of fixations during choice argued that these biases might result from flexible value updating in vmPFC and the ventral striatum, weighted by the current locus of attention (Lim et al., 2011). However, that analysis found that several other regions, including the VLPFC, precuneus and middle cingulate cortex, also showed this same effect. All patients in the current work showed some degree of fixation bias, arguing that this bias is robust to focal frontal lobe lesions. The work of Lim et al. (2011) suggests that ventral striatum is another plausible candidate source for this bias, a possibility that could be tested in patients with focal damage to this structure. Alternatively, the influence of fixations on choice might be the product of biased processing of decision options within a distributed network of brain areas. This interpretation implies that visual fixations have a feedforward influence, potentially tipping the scales in the competition between decision options at multiple levels of the choice process. By controlling the bottom-up weighting of visual information, fixations might influence competition between perceptual representations and action affordances linked to potential options. This account anticipates that these attentional effects should influence the balance of activity between associated actions, similar to the affordance competition hypothesis suggested by Cisek and Kalaska (2010). Magneto/electroencephalography (M/EEG) might help reveal how attention influences the processing of decision option at motor and perceptual stages on a much faster time scale than in the Lim et al. (2011) study, at least within the cerebral cortex.

The influence of fixations on choice was only increased in patients with DMF damage. This result demonstrates that this region mediates the influence of fixations on choice. In particular, damage to this region resulted in an apparent discounting of the unfixated option, such that subjects' choices were driven by the values of options that were currently being fixated rather than the relative value of both options. These results argue that DMF is critical to maintaining a representation of decision options that are currently unattended during a dynamic decision process. Transcranial magnetic stimulation (TMS) directed to DMF, and pre-SMA in particular, could be used to further test this hypothesis in healthy control subjects. Inhibition of this area would be expected to induce temporary discounting of the unfixated option, resulting in an increased likelihood of choosing the option that was currently fixated when the stimulation was delivered.

Recent work has shown that single unit and hemodynamic activity in dorsal ACC and dorsomedial PFC represent the value of exploring alternative options beyond the immediately available (i.e. 'default') choice (Hayden, Pearson, & Platt, 2011; Kolling et al., 2012; Quilodran et al., 2008). The results of the work presented here are in line with this notion; in particular, this work suggests that this coding might be dynamically dependent on the locus of attention. The immediately available choice might therefore be given greater attentional priority due to its status as the default option, although this coding could switch depending on the locus of attention. This hypothesis predicts that DMF damage would diminish foraging behavior, particularly when attention is devoted to the default choice.

The results presented here may also have relevance for interpreting findings from functional imaging studies. Many imaging studies have found that hemodynamic signals in

the dorsal ACC and dorsomedial PFC correlate with the value of the unchosen option, or negatively correlate with subjective value, while an opposite positive subjective value signal is frequently observed in vmPFC (Bartra et al., 2013; Blair et al., 2006). These subjective value signals in vmPFC depend on the locus of fixation, and reflect the attributes of decision options that are currently given priority (Hare, Malmaud, et al., 2011; Hunt et al., 2014; Lim et al., 2011, 2013). The results of Chapters 2 and 3 here are broadly consistent with a role for vmPFC in coding the value of attended option features, while the third study suggests that DMF may encode the value of unattended decision options. These results therefore suggest that the opponent coding of subjective value in dorsomedial PFC and vmPFC may relate to the locus of attention. This interpretation is also consistent with conflicting results from imaging work using foraging paradigms. Kolling et al. (2012) found that dorsal ACC activity was linearly related to the value of foraging, whereas vmPFC activity reflected the value of the default option. However, Shenhav et al. (2014) showed that as foraging values were increased beyond the range used by Kolling et al. (2012), the relationship between dorsal ACC activity and foraging value assumed an inverted 'U' shape. Importantly, attention would be expected to shift away from the default to the alternative ("forage") option as its value increases, potentially explaining the opposite pattern of activity observed by Shenhav et al. in this higher range.

Functionally, this deficit may also relate to the impairments in action selection also associated with DMF damage. Subjects with lesions to this region fail to rapidly correct motor errors in simple cue-based action selection tasks (Hochman, Wang, Milner, & Fellows, 2015; Modirrousta & Fellows, 2008; Swick & Turken, 2002; Wessel, Klein, Ott, & Ullsperger, 2014). These impairments might relate to a role for this region, particularly

SMA/pre-SMA, in overcoming automatic, stimulus-driven activation of action affordances in order to switch to an alternative response (Nachev, Kennard, et al., 2008). Other work has also found that these subjects are impaired in learning action-value associations (Camille, Tsuchida, et al., 2011). Complementary lesion work in monkeys suggests that the dorsal ACC is particularly critical in this form of learning (Rudebeck, Bannerman, & Rushworth, 2008). This region has a role in integrating representations of potential actions with subjective value (Rushworth et al., 2011), which might be vital for representing decision options or action affordances that are not currently attended, or are not explicitly cued or stimulus-bound.

Notably, the behavioral effects of DMF damage observed in this third study would not have been apparent simply from the choices and reaction times of these subjects, but were only evident after taking account of subjects' fixations. These results join a growing literature revealing how even seemingly basic decisions between options based on subjective value are influenced by attentional factors like preferential fixation time and visual saliency (Krajbich et al., 2010; Milosavljevic et al., 2012; Navalpakkam et al., 2010; Shimojo et al., 2003; Towal et al., 2013), and go further in revealing previously undetected effects of DMF damage on decision-making that were related to this bias. Increased fixation bias could be construed as a decision-making deficit that affects the maximization of values, as assessed by prior ratings. However this view ignores the possible positive effects that this bias might have in other settings where this behavior might be beneficial (e.g. exploitation of rewarding, attended options). While the normal fixation bias in other patient groups was described as reflecting intact behavior, this term is only meant to suggest that damage to these regions does not affect the extent of fixation-based value

updating. Overall, the results of this third study speak to the importance of measuring or controlling attentional factors in decision-making tasks, where they are more often than not left unconstrained.

The findings of this thesis have implications for understanding psychiatric disorders thought to involve frontal lobe dysfunction. While VMF damage affected attention to reward-predictive features, this behavior may be adaptive or maladaptive, depending on the context. Indeed, the behavior of VMF damaged subjects in study 1 could be construed as being 'better' than other groups, as these subjects were less affected by the distracting influence of reward associations that were incidental to the task. These same VMF-dependent processes may indeed be sub-optimal in other settings, as in attentional capture by stimuli with acquired incentive salience like drug or food cues in addiction and obesity (Robinson & Berridge, 1993; Volkow, Wang, Fowler, & Telang, 2008). Conversely, failure to direct attention to motivationally relevant cues might contribute to social and behavioral deficits in autism or schizophrenia (Klin, Jones, Schultz, Volkmar, & Cohen, 2002; Pelphrey et al., 2002; Streit, Wolwer, & Gaebel, 1997). Further work is necessary to determine whether VMF has a role in directing attention in these contexts, though a recent study suggests that VMF damage may affect attention to emotionally expressive faces (Wolf et al., 2014), a potential explanation for the facial emotion recognition deficits that have been described in these patients in past work (Heberlein, Padon, Gillihan, Farah, & Fellows, 2008; Jenkins et al., 2014; Tsuchida & Fellows, 2012).

The current thesis work may also relate to the neural mechanisms underlying simulation of potential positive outcomes. Previous work has shown that VMF damaged subjects tend to adopt a 'satisficing' strategy when exploring the attributes of decision

options (Fellows, 2006), and experience less regret for poor choices (Camille et al., 2004), though the anatomical basis of this reduction in regret has recently been disputed (Levens et al., 2014). These effects of VMF damage in patients might relate to the role of this region in simulating potential outcomes or counterfactuals that has been observed in rats (Steiner & Redish, 2014). Several neuropsychiatric disorders, (e.g. anxiety, depression and posttraumatic stress disorder) are marked by dysfunctional simulation of potential outcomes, which can have a debilitating, inhibitory effect on behavior (Clark, Chamberlain, & Sahakian, 2009; Epstude & Roese, 2008; Milad & Rauch, 2007). These maladaptive predictions may result in increased attention to negative stimuli, often seen in these disorders (Frewen, Dozois, Joanisse, & Neufeld, 2008; Peckham, McHugh, & Otto, 2010). Intriguingly, VMF damaged patients showed a tendency toward greater attentional bias to the low-reward color in Chapter 2, similar to an attentional bias away from rewarding or pleasant stimuli seen in depressed and high anxiety subjects (Frewen et al., 2008). Lesion studies might help determine whether VMF has a role in these symptoms, testing if damage to this region also affects the guidance of attention to stimulus features that predict negative outcomes.

This doctoral work also has clear relevance for understanding the functional deficits related to frontal lobe damage in neurological disorders. In the last 20 years, a great deal of effort has been made to better differentiate the deficits associated with damage to frontal lobe sub-regions using increasingly specific tasks (Glascher et al., 2012; Stuss & Levine, 2002; Tsuchida & Fellows, 2013). However, the mechanisms underlying these deficits remain poorly understood, particularly in the case of decision-making or reward learning impairments that are frequently associated with VMF damage. As a result, the ecological

significance of impairments in these tasks is hard to define, posing a problem for clinical interpretation of the significance of these impairments for daily functioning (Zald & Andreotti, 2010). The studies presented here examined whether these deficits were linked to attentional impairments. The findings argue that frontal sub-regions have mechanistically discrete roles in selecting features based on task relevance or reward value, and in representing unattended options. These results may support efforts to better define the features of decision-making affected in patients with frontal lobe damage due to injury or neurodegenerative disease. Neuropsychological tests focused on the mechanisms of decision impairment described here may give more insight into the challenges experienced by these patients outside of the laboratory or the clinic.

As with all investigations of brain lesions in human patients, the work presented here is limited by a number of practical considerations. In particular, the idiosyncratic nature of brain lesions in any given clinical sample, and potential effects of damage on underlying white matter, constrain the anatomical specificity of structure-function claims. While VLSM analysis may help in this regard, this method has its own limitations (i.e. lack of power, sensitivity to lesion covariance (Kimberg et al., 2007; Mah, Husain, et al., 2014)). Patients often also have comorbidities, and may be taking psychoactive medication, which could be confounding factors when comparing these groups to healthy controls. Despite these limitations, examining the effects of chronic brain lesions remains the strongest form of evidence for testing the necessity of a region for a particular behavior (Rorden, Fridriksson, & Karnath, 2009). Temporary inactivation methods, such as TMS, cannot be used to target ventral structures, such as VMF, in human subjects. Chronic lesions also provide more reliable tests of necessity, as temporary inactivation may result in acute

behavioral changes that rapidly dissipate when the disrupted neural circuit recovers (Otchy et al., 2015). Converging evidence from neuroimaging and animal models may help address the limitations of the current work. Future studies may further address these points by testing the relation of white matter damage to behavioral deficits (e.g. Thiebaut de Schotten et al., 2014), or the effects of damage on functional brain networks (e.g. Alstott, Breakspear, Hagmann, Cammoun, & Sporns, 2009), and how such changes relate to behavioral deficits. Such efforts may also help bridge increasingly network-oriented perspectives in cognitive neuroscience with the predominantly nodal approach of focal lesion studies.

In summary, this thesis demonstrates the critical contributions of different frontal sub-regions for mediating associative learning and decision-making through attentional mechanisms. The studies presented here support the notion that these sub-regions play distinct roles in this process, as evidenced by the different patterns of behavioral deficit related to focal lesion damage. This work opens new avenues of investigation that may address the bases of these attentional phenomena and their involvement in decision-making.

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