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Review article

Human lesion studies of ventromedial prefrontal cortex

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ABSTRACT

Studies of neurological patients with focal lesions involving ventromedial prefrontal cortex (vmPFC) have demonstrated a critical role for this brain area in various aspects of cognition, emotion, and behavior. In this article, we review the key themes, methods, and findings from neuropsychological research on vmPFC lesion patients. Early case studies demonstrated profound disruptions in personality and behavior following vmPFC damage, including blunted affect, poor decision-making, and inappropriate social behavior. Subsequent laboratory investigations with groups of vmPFC lesion patients have revealed deficits in a host of interrelated functions, such as value-based decision-making, future and counterfactual thinking, physiological arousal to emotional stimuli, emotion recognition, empathy, moral judgment, and memory confabulation. The compendium of findings described here demonstrates that vmPFC is crucial for diverse aspects of adaptive function.

1. Introduction

Dating back to the legendary case of Phineas Gage (Harlow, 1868), studies of humans with focal brain damage have yielded unique and foundational insight into the psychological and behavioral functions subserved by prefrontal cortex. In particular, human lesion studies have been pivotal in identifying the critical role of ventromedial prefrontal cortex (vmPFC) in various aspects of emotion, decision-making, social behavior, and memory. In this review article, we will summarize the major themes and findings of research on vmPFC lesion patients over the past several decades. First, we will briefly describe the anatomy of human vmPFC lesions. Next, we will survey the key findings from studies of these patients and consider several important caveats regarding vmPFC lesion characteristics. Finally, we will discuss the relevance of the reviewed data for theoretical models of vmPFC function.

Although recent review and commentary articles have considered the functions of vmPFC across multiple experimental approaches (including human lesions and functional neuroimaging as well as non-human animal lesions and electrophysiology) (Delgado et al., 2016; Roy et al., 2012) or have considered the effects of prefrontal damage more broadly (anatomically speaking) in human and non-human primates (Szczepanski and Knight, 2014), this review article is distinct in its specific focus on studies of focal vmPFC damage in humans. The intent of this article is not to exhaustively cite every study that has been published on vmPFC lesion patients; rather, the goal is to illustrate the major themes, findings, limitations, theoretical perspectives, and outstanding questions in this field of research. The cited studies were selected by the authors to accomplish this goal, based on their familiarity with and exploration of the extant research in this area, rather than on a pre-specified set of databases, search terms, and publication dates.

2. Anatomy of vmPFC lesions

In human lesion studies, “vmPFC” generally refers to the lower half of the medial prefrontal cortex (approximately below the level of the genu of the corpus callosum) and the medial sector of the orbital surface (the gyrus rectus and medial orbital gyri). This territory includes Brodmann areas 11, 12, 25, the subgenual portion of 32, and the lower medial portion of 10. It is important to note that the term “vmPFC” does not refer to a discrete brain structure with clearly defined and uniformly applied anatomical borders, such as a specific nucleus or gyrus. vmPFC lesions may span multiple Brodmann areas *within* an individual and include overlapping but distinct areas *between* individuals. Among the vmPFC lesion patients typically included in neuropsychological research studies, brain tissue damage most commonly results from surgically-resected tumors (particularly orbital meningiomas), subarachnoid hemorrhage (particularly from the rupture of aneurysms in the anterior communicating artery), ischemic stroke (particularly involving the anterior cerebral artery), or traumatic brain injury. Fig. 1 provides examples of the spatial distribution of lesions typically seen in vmPFC lesion studies.

As can be seen in Fig. 1, lesions in this region typically involve both the orbital and medial aspects. By contrast, human functional imaging

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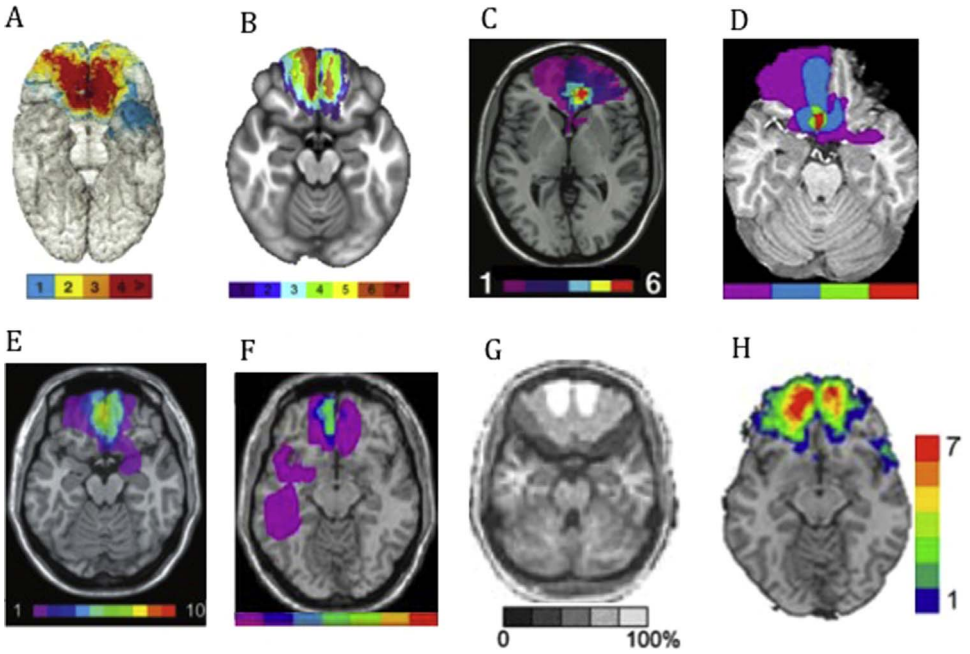

Fig. 1. Examples of lesion distributions ("lesion overlap maps") from studies of human vmPFC lesion patients. The color bars indicate the degree of overlap in each voxel (either the number of overlapping lesions at that voxel or the percentage of subjects from the vmPFC lesion group with damage to that voxel) **A.** Adapted from Bechara et al. (1998) (n = 9 bilateral vmPFC patients), **B.** Adapted from Wolf et al. (2016) (n = 7 vmPFC patients; n = 5 bilateral meningioma, n = 2 unilateral ACoA aneurysm), **C.** Adapted from Fellows and Farah (2007) (n = 10 bilateral vmPFC patients, n = 7 ACoA aneurysm, n = 3 stroke), **D.** Adapted from Ghosh et al. (2014) (n = 10 vmPFC patients, n = 10 ACoA aneurysm), **E.** Adapted from Ciaramelli et al. (2013) (n = 10 bilateral vmPFC patients, n = 6 ACoA aneurysm, n = 3 TBI, n = 1 tumor), **F.** Adapted from Shamay-Tsoory et al. (2012) (n = 8 vmPFC lesion patients, n = 1 bilateral CVA, n=7 unilateral TBI), **G.** Adapted from Beer et al. (2003) (n = 5 bilateral vmPFC patients, n = 5 TBI), **H.** Adapted from Koenigs et al. (2008) (n = 7 bilateral vmPFC lesion patients, n = 7 penetrating head-injury). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

studies typically yield activation loci within more circumscribed regions of vmPFC, and these activations can thus be reported with more specific anatomical terms such as "anterior medial orbitofrontal cortex" or "subgenual cingulate cortex". Similarly, non-human primate studies that target a specific sulcus, gyrus, or Brodmann area within vmPFC (e.g., with a focal lesion or recording electrode) may use those more specific anatomical terms. Owing to this greater spatial resolution, studies using these techniques typically reserve the term "vmPFC" to specifically refer to the ventral portion of medial aspect of PFC (e.g, Roy et al., 2012). For more detailed consideration of the morphological and cytoarchitectural features of vmPFC, see (Mackey and Petrides, 2014; Öngür et al., 2003; Ongür and Price, 2000).

3. Domains of dysfunction following vmPFC lesions

3.1. Personality

In the mid-1970s, Blumer and Benson (1975) described multiple cases of dramatic personality change following damage to the lower prefrontal cortex. These patients became apathetic, irritable, disinhibited, demonstrated brash social conduct, and suffered profound changes in decision-making often resulting in vocational and personal strife (Blumer and Benson, 1975). Despite these clear disruptions in behavior and significant changes in personality, standard neuropsychological measures revealed little to no intellectual deficit that could explain the abysmal judgment and maladaptive behavior of these patients (Blumer and Benson, 1975). The authors thus coined the term "pseudopsychopathy", likening the personality changes observed in these patients to the syndrome of psychopathy, which is characterized by shallow affect, callous lack of empathy, impulsivity, and irresponsibility (Hare, 2003).

In subsequent years, additional case studies presented patients with similar behavioral patterns following vmPFC damage (Andy et al., 1981; Cicerone and Tanenbaum, 1997; Eslinger and Damasio, 1985; Malloy et al., 1993; Shallice and Burgess, 1991). The case study of EVR provided a detailed account of the changes associated with damage to the vmPFC (Eslinger and Damasio, 1985). At age 35, EVR, a man with a history of prudent and responsible behavior personally and professionally, underwent surgery to remove a cerebral tumor, which resulted in a bilateral lesion involving the vmPFC (Eslinger and Damasio, 1985). Following the onset of the lesion, EVR developed profound difficulties in both his personal and professional life, comparable to those described previously (Blumer and Benson, 1975; Harlow, 1868): he fell out of work due to his unreliability and disorganization; he began a new ill-advised business venture which resulted in bankruptcy; his decades-long marriage soon ended and he quickly began a new short-lived relationship with a disreputable partner; and he was eventually forced to move in with his parents. The authors described EVR's constellation of personality and behavioral changes as "acquired sociopathy" (Eslinger and Damasio, 1985), paralleling Blumer and Benson's description of "pseudopsychopathy" (1975). Despite EVR's patently impaired function in everyday activities, he demonstrated intact or superior performance on virtually all conventional neuropsychological measures of language, intelligence, attention, and executive function. Corroborating these case studies, an examination of a larger group of bilateral vmPFC lesion patients identified several changes reliably associated with vmPFC damage: blunted emotional experience, irritability and poor frustration tolerance, defective decision-making, social inappropriateness, impaired goal-directed behavior, and lack of insight (Barrash et al., 2011, 2000). As will be detailed in the following sections, experimental studies have attempted to parse the precise psychological mechanisms that underpin the dramatic changes in personality and behavior exhibited by vmPFC lesion patients.

3.2. Decision-making

A conundrum facing clinical researchers in this area was how to reconcile the execrable real-world social behavior and decision-making of vmPFC lesion patients with their relatively intact performance on conventional neuropsychological measures of cognitive function. To address this apparent discrepancy, experimenters began developing more loosely-structured tasks designed to mimic aspects of real-world situations—a notable departure from the highly-structured testing commonly used in neuropsychology. For example, the multiple errands test requires participants to navigate through a shopping center and interact with other patrons in order to accomplish a list of errands that vary in terms of complexity (Shallice and Burgess, 1991). Relative to neurologically intact comparison subjects, three patients with damage to the frontal lobes—including but not limited to the vmPFC—performed poorly in the task, exhibiting inefficiency and rule-breaking (Shallice and Burgess, 1991). A subsequent investigation using the same task showed these deficits to be specifically associated with vmPFC

damage (Tranel et al., 2007). Other studies modeling real-world scenarios presented patients with tasks such as financial planning (Goel et al., 1997) and conducting apartment searches (Fellows, 2006). In the former task, vmPFC patients demonstrated impairments in producing viable solutions and implementing a feasible money-saving plan. In the latter task, vmPFC patients produced fewer feasible solutions (despite taking more time) than the neurologically healthy comparison group. In a more recent study, participants were tasked to present valid solutions to hypothetical situations presenting both social (e.g., addressing an angry friend at a party) and nonsocial (e.g., not having money to pay a restaurant bill) scenarios (Peters et al., 2017). vmPFC patients were less able to generate valid options to resolve the open-ended scenarios than were comparison groups. Convergent evidence thus suggests that vmPFC patients have trouble both generating feasible options and choosing the best decision.

In a related line of research, the Iowa Gambling Task (IGT) was developed to test the performance of vmPFC patients on a laboratory task that incorporates elements of reward, punishment, risk, uncertainty, and changing contingencies (Bechara et al., 1994). In this task, participants choose cards from four decks, with each card indicating a net gain or loss of money. The key manipulation is that the decks are programmed so two decks are "good" in the long run (i.e., continuous selection from these decks results in a net gain of money) while two decks are "bad" in the long run (i.e., continuous selection from these decks results in a net loss of money). So, through variable experiences of reward and punishment with each deck, the subject must formulate a plan of action that is advantageous in the long run (i.e., pick mostly from the good decks). Importantly, it is too difficult to consciously track the precise overall yield from each of the four decks, and therefore the task requires some other way outside of deliberate recollection to choose between the good and bad decks (Bechara et al., 1994). Over the course of the task, neurologically intact participants eventually begin avoiding the bad decks and selecting the good decks more frequently, while simultaneously generating skin conductance responses (SCRs) before selecting from the bad decks (Bechara et al., 1997). In contrast, vmPFC lesion patients continue to select from the bad decks, and do not generate the same anticipatory SCRs (Bechara et al., 1997). Recent studies have corroborated the IGT performance deficit in vmPFC patients (Abel et al., 2015; Sutterer et al., 2016) and have shown that this defect is stable over time (Waters-Wood et al., 2012; Xiao et al., 2013).

The exact mechanism(s) underlying the deleterious effect of the vmPFC on the IGT remains to be fully elucidated. Some authors have questioned whether the critical role of PFC in the IGT is restricted to the vmPFC, with multiple studies indicating that damage to the dlPFC can contribute to deficits in performance on the IGT (Clark et al., 2003; Fellows and Farah, 2005a; MacPherson et al., 2009; Manes et al., 2002; Ouerchefani et al., 2017). However, a distinct difference in the underlying cause for the deficit may explain the similar impact of vmPFC and dlPFC damage on this task. Evidence suggests damage to the dlPFC impacts performance on the IGT through overall decreased executive function, whereas the vmPFC has a unique impact on the participant's ability to accurately compute stimulus value (Fellows and Farah, 2005a). Additionally, a large study ($n = 344$) utilizing voxel-based lesion symptom mapping identified the critical neural substrates for a variety of executive function tests and the IGT, and found that IGT performance deficits are most strongly associated with damage to vmPFC, whereas executive function deficits are associated with damage to the dlPFC and anterior cingulate cortex (Gläscher et al., 2012). Thus, although lesions outside the vmPFC can impact executive functions that are related to IGT performance, evidence still suggests a unique role for the vmPFC in successful IGT performance.

Since the initial demonstration of impaired performance on the IGT, a host of studies have shown the effects of vmPFC damage on value-based decision-making. These studies suggest that damage to the vmPFC impairs the ability to maintain stimulus value (Camille et al., 2011a, 2011b; Fellows and Farah, 2007; Koenigs and Tranel, 2008). For example, damage to the vmPFC disrupts normal preferences based on commercial brands, (Koenigs and Tranel, 2008); maintenance of simple binary preferences for basic items (e.g., famous people, food, and colors) (Fellows and Farah, 2007); and value maximization for stimuli (e.g., if someone prefers X over Y and Y over Z, the individual should consistently choose X over both Y and Z and Y over Z) (Camille et al., 2011a). Furthermore, studies of "reversal learning" show that vmPFC damage impairs the ability to flexibly adjust the pattern of behavioral responses when stimulus values change, or "reverse" (Fellows and Farah, 2003; Hornak et al., 2002). Similarly, patients with vmPFC damage struggle to select the most advantageous decks in a probabilistic learning task, where participants select between two decks that differ in terms of win probability (Tsuchida et al., 2010). Relative to comparison groups, vmPFC patients are impaired in learning the initial associations as well as switching their pattern of selections following reversal. In another probabilistic feedback task, vmPFC patients also fail to avoid a stimulus paired with negative feedback (Wheeler and Fellows, 2008). Interestingly, this association may be specific for valuing items, but not actions. One study found that vmPFC damage disrupts stimulus valuation (e.g., distinguishing between decks that result in gains versus losses) but leaves intact the ability to compute the same comparison with actions (e.g., selecting between two different hand motions) (Camille et al., 2011b). A recent study also demonstrates that vmPFC damage disrupts the ability to adjust goal-directed decision-making after reward devaluation (Reber et al., 2017). In this study, unlike comparison groups, vmPFC patients continued to select food items on which they had been satiated.

The deficit in decision-making associated with vmPFC damage has also been framed as impaired future thinking and an inability to anticipate future consequences following a decision. For example, the IGT deficits of patients with vmPFC damage were initially interpreted as an inability to account for future consequences of behavior (Bechara et al., 2000, 1994). A later study tested the ability of vmPFC patients to generate future life events, showing the vmPFC lesion patients produce events chronologically closer in the future than do comparison groups (Fellows and Farah, 2005b). Another study investigated future thinking through a delayed-gratification task, showing that the effect of temporal discounting (e.g., the decrease in reward value as the time between task and reward increases) is enhanced in vmPFC patients (Sellitto et al., 2010). The anticipation for future consequences further relates to counterfactual thinking and evaluating hypothetical scenarios (Barbey et al., 2009; Beldarrain et al., 2005; Camille et al., 2004). vmPFC patients express diminished ability to conjure both future and imaginary scenarios (Bertossi et al., 2016, 2015). This inability could explain the increased susceptibility to the "reflection effect" in decision-making exhibited by patients with vmPFC damage (Pujara et al., 2015). The "reflection effect" refers to the tendency to prefer sure amounts over risky gambles in situations involving potential gain, but to prefer risky gambles over sure amounts in situations involving potential loss (Tversky and Kahneman, 1985). The enhanced reflection effect among vmPFC patients could result from a diminished emotional reaction to the hypothetical outcome of a gamble, which would lead vmPFC patients' decisions to be governed more by their reactions to the sure options (i.e., reduced attraction to potential gains in the gamble and reduced aversion to potential losses in the gamble) (Pujara et al., 2015). Finally, damage to the vmPFC increases risk-taking behavior, with vmPFC patients choosing the more risky options at higher rates than other brain-damaged patients and normal comparison groups (Clark et al., 2008; Floden et al., 2008; Sanfey et al., 2003).

3.3. Emotion expression

As described above, one of the most striking changes resulting from vmPFC damage relates to the expression of emotion—apathy, blunted affect, lack of empathy, irritability, and erratic emotion regulation

(Blumer and Benson, 1975; Eslinger and Damasio, 1985; Knutson et al., 2015, 2014; Meyers et al., 1992; Shallice and Burgess, 1991). Laboratory studies of emotion expression in vmPFC lesion patients have employed a number of self-report, task performance, and peripheral physiological measures. One of the earliest such studies measured skin conductance while subjects viewed emotionally evocative pictures, and found blunted SCRs in vmPFC lesion patients compared to other brain-damaged patients and neurologically intact individuals (Damasio et al., 1990). This psychophysiological deficit also extends to the anticipation of startling sounds (Roberts et al., 2004) and listening to emotionally evocative music (Johnsen et al., 2009). Damage to the vmPFC may also disrupt feelings of regret; in a study in which subjects chose between two gambles, the vmPFC lesion group reported diminished feelings of regret and reduced SCRs after receiving feedback that the unchosen gamble had a better outcome than the gamble they selected (Camille et al., 2004). Consistent with these findings, another study found that vmPFC lesion patients report sharp decreases in the subjective feeling of negative emotions (Hornak et al., 1996). However, a more recent study reported that vmPFC lesion patients endorse normal subjective emotional responses to laboratory inductions of different moods, and contrary to the studies described above, increased negative affect in overall disposition (Gillihan et al., 2011). Additionally, a recent study found normal experiences of regret among vmPFC lesion patients in response to losses in gambling scenarios (Levens et al., 2014). One possible explanation for this discrepancy is the anatomical distribution of lesions in each study. Whereas the Camille et al. (2004) study included patients with damage to the vmPFC extending into the surrounding lateral orbitofrontal cortex (LOFC), the Levens et al. (2014) study included a vmPFC patient group with no overlap in the LOFC, along with an additional LOFC lesion group. The LOFC lesion group had impaired experiences of regret in this task, suggesting the results in Camille et al. (2004) could be explained by the inclusion of patients with damage extending in to the LOFC. Another potentially important distinction in this area of research is between emotional responses that are elicited by an immediate event (e.g., losing money) versus those that are elicited by the anticipation of the event (e.g., the prospect of losing money). Bechara and Damasio (2005) have proposed that vmPFC is critical for the latter but not the former.

Additional evidence supporting the effect of vmPFC damage on blunting the expression of emotion comes from studies demonstrating a reduced likelihood of developing mood and anxiety disorders following damage to the vmPFC. Within a sample of Vietnam War veterans who suffered brain damage from penetrating head injuries during combat, subjects with damage to the vmPFC had reduced rates of depression and PTSD when compared to other veterans who were either neurologically intact or had damage to other regions of the brain (Koenigs et al., 2008, 2007a). When reporting specific symptoms of depression, vmPFC patients endorsed normal levels for “somatic” symptoms of depression such as fatigue, changes in appetite, and sleep disturbance, but markedly decreased levels of “cognitive/affective” symptoms like feelings of sadness, guilt, and worthlessness (Koenigs et al., 2008). These lesion findings are germane to “psychosurgery” approaches to severe, refractory depression and other mental illness, which have included the selective lesions of vmPFC and/or its subjacent white matter (Poynton et al., 1995; Sachdev and Sachdev, 2005). In some cases, these surgical lesions have been credited with markedly reducing negative affect in severely ill patients. (Sachdev and Sachdev, 2005), underscoring the profound effect of vmPFC damage on the expression of emotion.

3.4. Social cognition

A number of investigations have explored and elaborated on the marked changes in social behavior observed in vmPFC lesion patients. One unique study required subjects to interact with a stranger (actually a study confederate) (Beer et al., 2003). vmPFC lesion patients engaged in behaviors judged by the researchers as socially inappropriate more often than did a neurologically intact group; specifically, patients used more inappropriate nicknames, engaged in overly familiar interactions, such as disclosing highly private information (e.g., “I felt guilty when I cheated on my wife”), and made prolonged eye contact. Other studies have involved more hypothetical situations. In a questionnaire about scenarios designed to elicit disgust, vmPFC patients were less likely to avoid engaging in hypothetical behaviors eliciting interpersonal disgust (e.g., “using the scarf from a busker”) relative to both neurologically intact and brain-damaged comparison subjects (Ciaramelli et al., 2013). Another study found that vmPFC patients are impaired in the ability to interpret relationships between people from watching video clips of social interactions (Mah et al., 2004).

Building on the social deficits observed in the everyday behavior of vmPFC lesion patients, a host of laboratory studies have examined the effect of vmPFC damage on the ability to recognize and understand the emotions of others. An early study contrasting the performance of patients with ventral frontal damage (including vmPFC) to patients with damage to other regions of the brain revealed severe impairments in the identification of facial expressions of emotion (Hornak et al., 1996). The patients with ventral frontal damage were also impaired in identifying emotion from vocal expression (Hornak et al., 1996). More recent studies of bilateral vmPFC lesion patients have expanded upon this initial finding, revealing diminished recognition accuracy across different emotional valences, and specifically in negative valence emotions (Heberlein et al., 2008; Monte et al., 2013; Tsuchida and Fellows, 2012; Vandekerckhove et al., 2014). For example, in one study the vmPFC lesion group rated faces expressing fear and disgust with the least consistency (Heberlein et al., 2008). A follow-up study found decreased performance in the vmPFC lesion group on distinguishing subtle facial expressions of emotion from neutral faces, when compared to a neurologically healthy group and patients with more dorsal and lateral frontal damage (Tsuchida and Fellows, 2012). Another study of vmPFC lesion patients found the recognition deficit for anger, disgust, fear, and sadness (Monte et al., 2013), while another study found the deficit specific to fear and anger, with more incorrect interpretations of surprise (Vandekerckhove et al., 2014). A subsequent eye-tracking study showed that vmPFC lesion patients make a smaller proportion of fixations to the eyes of the stimuli during a facial emotion recognition task, suggesting that the vmPFC is critical for guiding visual attention to correctly identify emotions (Wolf et al., 2014). Further investigation revealed that emotion recognition deficits in vmPFC lesion patients can be ameliorated by instructing subjects to attend to the eyes of the stimulus (Wolf et al., 2016).

A related line of research on social cognitive abilities has investigated the effect of vmPFC damage on a host of measures related to empathy and theory of mind (ToM). One study found that vmPFC lesions are associated with decreased endorsement of spontaneous perspective-taking and emotional contagion as indicated by self-report measures (Shamay-Tsoory et al., 2004). However, a follow-up study using a self-report scale found vmPFC patients selectively endorse lower spontaneous perspective taking, but intact emotional contagion (Shamay-Tsoory et al., 2009). Additionally, a separate patient group with damage of the inferior frontal gyrus endorsed reduced emotional contagion and intact perspective taking, suggesting an anatomical dissociation between these two aspects of empathy (Shamay-Tsoory et al., 2009). A later study utilizing voxel-based lesion symptom mapping associated damage to lateral orbital prefrontal regions with deficits in self-reported emotional contagion, while vmPFC damage was not associated with such deficits (Driscoll et al., 2012).

Studies employing performance-based tasks of empathy and ToM have further elucidated deficits in social cognition associated with vmPFC lesions. Studies using faux pas recognition tasks have demonstrated a reliable deficit in vmPFC patients in correctly identifying others’ embarrassment (Bird et al., 2004; Shamay-Tsoory et al., 2005; Stone et al., 1998). Additionally, vmPFC patients perform poorly on tests of second-order false belief tasks (i.e., inferring someone's

thoughts based on the thoughts of someone else) (Shamay-Tsoory et al., 2009, 2006, 2005; Shamay-Tsoory and Aharon-Peretz, 2007; Stuss et al., 2001). These deficits may be particularly pronounced for ToM tasks involving affective information. For example, while vmPFC patients exhibit normal performance in second-order false belief tasks involving emotionally neutral events, vmPFC patients perform poorly on such tasks involving affective information (i.e., understanding what someone thinks about how someone else feels) (Shamay-Tsoory et al., 2006, 2005; Shamay-Tsoory and Aharon-Peretz, 2007). Moreover, in a battery of ToM tasks including emotional and non-emotional trials of irony identification, false attribution, understanding lies, and false belief tasks, vmPFC patients performed worse than other frontal patients and healthy comparisons only on the emotional items, with intact performance on the non-emotional items in each task (Shamay-Tsoory et al., 2006). Overall, the vmPFC seems to be particularly critical for spontaneous perspective taking and ToM tasks involving affective information.

A separate aspect of social cognition that has been studied in vmPFC lesion patients is morality and moral judgments. In one classic paradigm involving "trolley dilemmas" (Thomson and Parent, 1986), subjects must decide whether to inflict a direct, intimate, physical harm to another person in order save a greater number of individuals from harm (the "utilitarian" response). In hypothetical scenarios, vmPFC lesion patients rate the utilitarian harm as more morally permissible than do brain-damaged and neurologically healthy comparison subjects (Ciaramelli et al., 2007; Koenigs et al., 2007b; Thomas et al., 2011). Additionally, vmPFC lesion patients exhibit blunted SCRs compared to brain-damaged and neurologically intact comparison groups while endorsing such harms (Moretto et al., 2009), suggesting that a diminished affective response to the personal harms may underlie the utilitarian moral judgments in these patients. In a separate paradigm that assesses the relative weight of intentions and outcomes in moral judgments, vmPFC patients base their moral judgments more on the outcome of scenarios (i.e., rated failed attempts to harm as more morally permissible) relative to brain-damaged and healthy comparison subjects (Ciaramelli et al., 2012; Young et al., 2010). This finding suggests that vmPFC is critical for integrating the beliefs or intentions of others into moral judgment. Furthermore, damage to the vmPFC is associated with increased belief in authoritarian and fundamentalist constructs, suggesting once again a disruption of moral and ethical judgments following vmPFC damage (Asp et al., 2012).

Another set of studies on social behavior following vmPFC damage has employed economic exchange paradigms. Studies of the Ultimatum Game have shown that vmPFC lesion patients are more likely to reject unfair (but financially advantageous) monetary offers (Koenigs and Tranel, 2007; Shamay-Tsoory et al., 2012). However, this effect is diminished when the salience and immediacy of the monetary outcome is increased (Moretti et al., 2009). Other economic exchange games have shown that vmPFC patients are less generous in terms of sharing money with anonymous partners (Dictator Game) and less trustworthy for repaying money to anonymous partners (Trust Game) (Krajbich et al., 2009).

3.5. Memory

Apart from the social and emotional deficits described to this point, damage to the vmPFC has also been associated with alterations in memory, particularly with regard to confabulation (i.e., false memory retrieval without the conscious intention to deceive). A number of studies have documented confabulation in patients with vmPFC damage (Benson et al., 1996; Mercer et al., 1977; Moscovitch and Melo, 1997). For example, when asked to retrieve a memory based on a word cue, patients with damage to the vmPFC were more likely than a brain-damaged comparison group to confabulate (Moscovitch and Melo, 1997). Moreover, in a battery of questions designed to test confabulation (e.g., questions about personal semantic and episodic memories), vmPFC patients consistently confabulated more frequently than a group of frontal patients with damage outside the vmPFC (Turner et al., 2008).

A possible mechanism for why vmPFC damage results in confabulation is the inability to suppress irrelevant memories and memory schemas (Burgess and Shallice, 1996). For example, confabulating patients with damage including the vmPFC make more false positive errors on a memory recognition task, suggesting the vmPFC is involved in suppressing irrelevant information in memory (Schnider and Ptak, 1999). Other studies have specifically tested the role of the vmPFC in memory schema. A memory schema is an organized group of past experiences and associations, which become active depending on context to help inform decisions and make predictions (Ghosh and Gilboa, 2014; Hebscher et al., 2016). A study investigated how well vmPFC lesion patients with a history of confabulation determine the relevance of a word to an imagined scenario (e.g., "going to bed"), and then determine the relevance of the same list of words to a second separate scenario (e.g., "visit to the doctor") (Ghosh et al., 2014). When assigning words to the second scenario, the vmPFC patients with a history of confabulation were more likely to assign words from the first scenario as relevant in the second, indicating a failure to suppress the schema of the first scenario when evaluating relevance to the second scenario.

Similarly, other studies have tested the influence of environmental context on memory in vmPFC patients (Spalding et al., 2015). Whereas neurologically healthy and brain-damaged comparison groups perform better in a memory recognition task when in the same context as learning, vmPFC lesion patients do not show the same enhanced context effect. Another task examined the influence of semantically similar words on false positive rates of recognition, and found that patients with vmPFC damage do not demonstrate the increased false positive rate seen in the normal comparison group (Warren et al., 2014). Together, these studies suggest a critical role for vmPFC in integrating context with current mental states or task goals, and could thus contribute to deficits seen in other domains of functioning like decision-making (Euston et al., 2012; Hebscher and Gilboa, 2016; Nieuwenhuis and Takashima, 2011).

4. Lesion characteristics

While the preceding sections have summarized general relationships between vmPFC damage and deficits in various domains of cognition and behavior, there are important caveats regarding the characteristics of the lesion sample that may impact the types and severity of behavioral deficits observed following injury. In this section we review several of these factors.

4.1. Etiology

vmPFC lesions may arise from a variety of etiologies, the most common of which are meningiomas (and associated neurosurgical resection to remove the tumor), cerebrovascular accidents (CVA) such as ischemic strokes or subarachnoid hemorrhage, and traumatic brain-injury (TBI) (Damasio, 1996). Each individual type of damage has varying advantages and disadvantages for use in neuropsychological study. Meningiomas arising from the anterior skull base can result in bilateral vmPFC damage that is generally stable after the acute stage of recovery (Abel et al., 2015; Damasio, 1996). The disadvantage to using tumor patients is the slow progression of tissue damage as the tumor grows, which can facilitate plasticity and compensation for dysfunction in and around the affected area (Desmurget et al., 2007). CVAs, on the other hand, can produce focal, stable lesions over a much shorter timespan. CVAs resulting in vmPFC damage include occlusion of the anterior cerebral artery (ACA), although lesions resulting from ACA strokes are typically lateralized to one side (Damasio, 1996). Additionally, the rupture of an aneurysm in the anterior communicating

artery (ACoA) may result in subarachnoid hemorrhage and vmPFC damage, but these lesions may be diffuse, and visualization of the damage may be impeded by artifact on the CT or MRI data due to the metal clip inserted to close the rupture (Damasio, 1996). Finally, while damage from TBI may include tissue loss in vmPFC, TBI typically includes more widespread neuropathology, including diffuse axonal injury (Johnson et al., 2013), hence the observed deficits or changes in these patients may not be solely or primarily attributable to vmPFC damage. The differences in lesion distribution resulting from these different etiologies can be seen in Fig. 1. Note for example how samples consisting primarily of orbital meningioma cases involve more bilateral and anterior lesions, whereas samples consisting primarily of ACoA aneurysm cases involve more posterior and unilateral lesions, and samples containing TBI cases involve more spatially diffuse lesions.

Despite these differences, a recent study directly investigating the effects of different etiological mechanisms of the frontal lobe damage on cognitive function provides support for combining different patient types in group studies. The authors investigated the impacts of CVA, low- and high-grade tumors, and meningioma on classic neuropsychological measures of frontal lobe function. Their results indicated no differences between the groups on the Raven's Advanced Progressive Matrices, Stroop, Letter Fluency, or Trail Making tests (Cipolotti et al., 2015). However, other studies have yielded evidence of differences in functioning following frontal lobe damage attributed to tumor-grade (Shallice et al., 2010; Talacchi et al., 2011) and between tumors and CVAs (Anderson et al., 1990). These unresolved questions warrant further investigation and highlight the importance of reporting lesion etiology when describing participants in vmPFC lesion studies. One possibility for clarifying the effect of lesion etiology/location across studies would be for investigators to routinely report anatomical coordinates for individual subject lesions or upload individual lesion masks, such that group lesion overlaps could be recreated in common virtual anatomical space for the purposes of quantitative analyses (akin to how the reporting of anatomical coordinates of fMRI activation loci facilitate quantitative meta-analyses).

4.2. Age of onset

In studies of neurological damage, age of lesion onset may be a critical factor in determining the degree of chronic functional impairment, as mechanisms of neurodevelopment and plasticity change across the lifespan. While the changes in personality and decision-making due to adult-onset vmPFC lesions have been described in the preceding sections, there are accumulating data to suggest that early-onset vmPFC damage (i.e., during infancy or early childhood) may result in more severe functional impairments. In a classic case study, a patient (J.P.) with congenital degradation of the bilateral frontal lobes expressed improper social conduct and disregard for safety from an early age (Ackerly and Benton, 1948; Anderson et al., 2009; Eslinger et al., 2004). As J.P. aged through childhood into adolescence, this abnormal behavior grew to include incessant lying, public sexual deviancy, auto theft, physical fights, and eventual expulsion from school, despite average intellectual abilities (Anderson et al., 2009; Eslinger et al., 2004). Subsequent case studies have demonstrated a remarkably consistent pattern of maladaptive behavior following early-onset vmPFC damage that persists into adulthood (e.g., severely impaired social behavior and decision-making, impulsivity, and emotional instability), with relatively normal scores on tests of intelligence and cognitive ability (Anderson et al., 1999).

More recently, laboratory paradigms have been employed to examine the effect of early-onset vmPFC damage on social cognition. Using the same task previously demonstrating abnormally utilitarian moral judgments in hypothetical scenarios by adult-onset vmPFC patients (Koenigs et al., 2007b), Taber- Thomas et al. (2014) showed that early-onset vmPFC lesions are associated with endorsement of moral violations that are more severe than those endorsed by the adult-onset vmPFC lesion group (e.g., brazenly self-serving violent actions). This finding indicates that vmPFC is critical for the acquisition and maturation of moral judgment, and suggests a potential neuropsychological mechanism by which early-onset vmPFC damage grossly impairs social conduct.

4.3. Laterality

Lesion laterality is another important consideration in the study of vmPFC lesion patients. The specialization of function between the left and right hemispheres is a fundamental feature of functional brain anatomy. While prefrontal functions may not be as clearly lateralized as sensory, motor, or language functions, there is preliminary evidence suggesting that unilateral vmPFC lesions may have different effects, depending on the hemisphere involved. Early case studies describing the “pseudopsychopathy” syndrome resulting from vmPFC damage typically described patients with substantial bilateral damage (Blumer and Benson, 1975; Eslinger and Damasio, 1985; Shallice and Burgess, 1991), though subsequent case studies have presented patients with similar personality and decision-making disturbances resulting from focal damage involving the vmPFC in either the left (Goldstein et al., 1993; Meyers et al., 1992) or right (Tranel et al., 2002) hemisphere only. Laboratory task paradigms have yielded similarly mixed results. IGT deficits have been reported for patients with right vmPFC damage (Manes et al., 2002), while other studies report IGT deficits in patients with left vmPFC damage (Mattavelli et al., 2012), and others report no lesion laterality with respect to IGT deficit (Ouerchefani et al., 2017). A study of emotional empathy reports deficits lateralized to the right vmPFC (Shamay-Tsoory et al., 2003), whereas a study of faux pas recognition (ToM) reports deficits only for the left vmPFC damage (Leopold et al., 2012). One interesting possibility is that the lateralization of vmPFC function may relate to gender; disruptions of social, emotional, and decision-making function have been reported for right-sided lesions in men with vmPFC damage, but in women only left-sided vmPFC damage results in comparable deficits (Reber and Tranel, 2017; Sutterer et al., 2015; Tranel et al., 2005). Based on these conflicting findings, additional research is needed to investigate the lateralization of different domains of vmPFC function. In particular, a greater number of sufficiently powered studies with *a priori* hypotheses regarding laterality will be important to more firmly establish laterality effects in this patient population.

5. Theories of vmPFC function

The diverse array of human vmPFC lesion findings reviewed in this article begs the question: What is the essential function (or functions) of vmPFC that is critical to the individual abilities impaired by vmPFC damage? Is there a single meta-function of vmPFC, or are there subregions within vmPFC that are specialized for the individual functions reviewed here? In this section, we describe theoretical perspectives on vmPFC function and evaluate how extant human lesion data support or challenge each model.

A number of theories of vmPFC function have centered on the generation and regulation of emotion. One of the early and most influential such theories, the “Somatic Marker Hypothesis” (Damasio et al., 1996), explains the decision-making deficits observed in vmPFC lesion patients in terms of their affective deficits (Bechara and Damasio, 2005). The theory proposes that decision-making is influenced by “somatic markers”—signals arising from bioregulatory processes, including emotions. Since vmPFC is the critical neural substrate for triggering somatic markers by linking knowledge about potential decision outcomes with the associated emotional responses, vmPFC lesion patients lack critical affective input during decision-making (Damasio et al., 1996). This theoretical framework attributes to vmPFC a particular role in generating emotional responses to “secondary inducers” (e.g., thoughts or memories of emotional situations), as opposed to

"primary inducers" (e.g., innate or learned stimuli that automatically trigger emotional responses when in the immediate environment) (Bechara and Damasio, 2005). Empirical support for the Somatic Marker Hypothesis has been obtained from a variety of studies of vmPFC lesion patients (each described in greater detail above): diminished peripheral physiological responses to affective stimuli (Damasio et al., 1990), performance deficits and diminished anticipatory physiological responses during the IGT (Bechara et al., 1997; but see also Dunn et al., 2006), abnormally "utilitarian" moral judgments in trolley-type scenarios (Koenigs et al., 2007), and abnormally low Dictator Game offers (Krajbich et al., 2009).

However, the Somatic Marker Hypotheses does not address two critical sequelae of vmPFC damage. First, vmPFC lesion patients exhibit deficits in a number of tasks that involve neither value-based choice nor affective response, such as the confabulation, schema, and recall/recognition tasks described above in the "Memory" section. Second, in addition to exhibiting diminished levels of certain emotional responses (e.g., guilt, empathy, embarrassment), vmPFC lesion patients also exhibit exaggerated levels of anger, frustration, and irritability. Indeed, dysregulated anger and frustration has been proposed as the primary explanation for vmPFC patients' abnormally high rates of rejection of unfair Ultimatum Game offers (Koenigs and Tranel, 2007). As an attempt to reconcile these ostensibly conflicting findings (i.e., "hypoemotional" responses in the trolley-type moral judgment task and Dictator Game, but "hyperemotional" responses in the Ultimatum Game), Koenigs et al. (2010) proposed that vmPFC may be critical for self-insight and self-reflection related to affective state. In situations of frustration or irritation (e.g., unfair Ultimatum offers), one might feel an impulse to respond aggressively or retributively (e.g., reject the offer). Koenigs et al. propose that psychologically and neurologically healthy individuals can recognize this impulse, reflect on the consequences of losing their temper in terms of social relationships or material considerations, and manage to modulate their response to some degree (e.g., accept the offer). Furthermore, they propose that the deployment of certain prosocial emotions, such as empathy and guilt (which are presumed to motivate non-utilitarian moral judgments and Dictator offers), is also dependent on processes of self-insight and reflection. Each of these emotions is derived from a concern for one's actions relative to others—they are defined by their social nature (Beer et al., 2003). If one has no insight or reflection upon how his or her actions will affect others or be construed by others, then these prosocial emotions may be conspicuously diminished. This perspective thus posits that a basic deficit in processes of self-insight and self-reflection could theoretically underlie both types of affective deficit (exaggerated anger/irritability and diminished empathy/guilt), and by extension the reduced Ultimatum acceptance rates, reduced Dictator proposals, and increased utilitarian moral judgments that have been observed in vmPFC lesion patients. A deficit in self-insight, which is manifest in the everyday behavior of vmPFC lesion patients (Barrash et al., 2000), has also been demonstrated experimentally as a key factor in the patients' deficits in social emotions, such as embarrassment (Beer et al., 2006).

A more recent emotion-centered theory of vmPFC function proposes that vmPFC is critical for "affective meaning", in that it is essential for affective physiological and behavioral responses driven by conceptual information, as opposed to more simple forms of affect, valuation, and affective learning (Roy et al., 2012). Although this general description closely corresponds to the "secondary inducer" concept of the Somatic Marker Hypothesis, Roy et al. explain how this conception of vmPFC function applies to a broader set of experimental conditions, including well-established paradigms from the human literature, such as placebo analgesia and emotion reappraisal, as well as from non-human animal literature, including fear extinction recall and reinforcer devaluation.

A second set of theories focuses more specifically on the role of vmPFC in the representation of subjective value (Fellows, 2011; Grabenhorst and Rolls, 2011; Levy and Glimcher, 2012; O'Doherty, 2011). This viewpoint is supported by a host of vmPFC lesion studies demonstrating deficits in value-based decision-making, including simple preference judgments, value maximizing choices, and value learning (reviewed by Fellows, 2011), however, other studies have shown consistent value ratings and value-based choices in these patients (Vaidya and Fellows, 2015). Although this value-representation perspective is not necessarily intended to provide a comprehensive overarching theory of vmPFC function, it is relevant to consider whether this perspective on vmPFC function could explain deficits that are ostensibly "emotional" and/or "social" in nature, at least in certain contexts. For example, a study manipulating the salience and immediacy of monetary outcomes in the Ultimate Game suggests that the reduced Ultimatum acceptance rates previously observed in vmPFC lesion patients are driven by degraded valuation of abstract, delayed rewards, rather than by poorly modulated anger toward another person (Moretti et al., 2009).

The aforementioned theories, which focus primarily on affective function and value-based decision-making, do not directly address the memory impairments observed in vmPFC lesion patients. Connecting these domains, Euston et al. (2012) propose that the essential function of mPFC (including vmPFC) is to learn associations between context, locations, events, and corresponding adaptive responses, particularly emotional responses. According to this model of mPFC function, deficits in both memory and decision-making tasks may be due to the fact that almost all such tasks entail the ability to recall the best action or emotional response to specific events in a particular place and time. Focusing more specifically on memory function, Ghosh et al. (2014) propose a critical role for vmPFC in instantiating associative networks of knowledge extracted over multiple similar experiences, termed "schemas". One intriguing possibility is that the social, emotional, and value processing functions that are so conspicuously affected by vmPFC damage may all be subsumed under a broader (and as yet underspecified) integration-type function concerning conceptual knowledge and schematic memories.

Another set of perspectives on vmPFC function highlights specialized subregions or gradients within vmPFC. Rather than posit a single primary, overarching function of vmPFC, these parcellation schemes propose multiple functionally specialized and anatomically discrete subregions within vmPFC. One subregion scheme distinguishes a more anterior/perigenual region of vmPFC from a more posterior/subgenual region based on emotional valence, with the anterior region associated with positive valence (e.g., reward, value) and the posterior region associated with negative valence (e.g., threat, fear) (Myers-Schulz and Koenigs, 2012; Roy et al., 2012). Roy et al. (2012) also propose a more nuanced scheme, with a relatively rostral and dorsal subregion (primarily anterior to genu of the corpus callosum) associated with emotion, autonomic, and reward functions, and a relatively caudal and ventral subregion (primarily inferior to the genu of the corpus callosum) associated with memory functions. In this analysis, social cognition and self-processing were related to both subregions. A separate subregion scheme proposes that, while both medial and orbital subregions of vmPFC encode value, orbital neurons are more sensitive to external factor such as visual cues, whereas medial neurons are more sensitive to internal factors such as satiety (Bouret and Richmond, 2010). Another perspective on functional specialization within vmPFC concerns the degree of abstraction of value representation. An early meta-analysis of human fMRI data proposed an anterior-posterior gradient, in which more abstract reinforcers such as money are represented more anteriorly than primary reinforcers such as taste (Kringelbach and Rolls, 2004). Given the limitations in spatial resolution afforded by naturally occurring lesions, it will be challenging to test these vmPFC subregion models in human lesion patients, however, we believe that this is a critical area for future investigation.

6. Summary and conclusion

In sum, the past several decades have seen remarkable progress in

the study of vmPFC lesion patients, from case reports documenting personality and behavioral changes to laboratory studies of patient groups involving sophisticated paradigms of value-based decision-making, emotion-related psychophysiology, and social cognition. Collectively this line of research has established the crucial role of vmPFC in a multitude of complex psychological functions that underlie adaptive human behavior. However, fundamental questions remain unanswered regarding the essential overarching function of vmPFC and its subregion architecture. Given the spatial and temporal limitations inherent to the study of human lesion patients, it will be necessary to bring a wider array of experimental approaches to bear on these questions. Nonetheless, the study of human vmPFC lesion patients will continue to provide a unique and indispensable source of knowledge regarding the biological basis of human cognition, emotion, and social behavior.

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