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Beyond a rod through the skull: A systematic review of lesion studies of the human ventromedial frontal lobe

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ABSTRACT

Neuropsychological studies from the past century have associated damage to the ventromedial frontal lobes (VMF) with impairments in a variety of domains, including memory, executive function, emotion, social cognition, and valuation. A central question in the literature is whether these seemingly distinct functions are subserved by different sub-regions within the VMF, or whether VMF supports a broader cognitive process that is crucial to these varied domains. In this comprehensive review of the neuropsychological literature from the last two decades, we present a qualitative synthesis of 184 papers that have examined the psychological impairments that result from VMF damage. We discuss these findings in the context of several theoretical frameworks and advocate for the view that VMF is critical for the formation and representation of schema and cognitive maps.

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Lesion; vmpfc; systematic review; schema; state

Introduction

On a fall day in 1848, outside a quiet little town in Vermont, an explosion rocked the railway track tucked among green woods. The town doctor, John Harlow, was quickly summoned to the boarding house where the patient was taken in an ox-cart, and Harlow was faced with the astonishing sight of a man who had a round iron rod rammed clean through the skull from jaw to crown. Far from being dead, the patient spoke, and expressed that "he hoped that he was not much hurt" (Harlow, 1868). Phineas Gage recovered, and though his intellectual faculties and speech remained intact, he underwent a seemingly drastic change in personality and manner—from a responsible, well-liked foreman to an ill-tempered and capricious scoundrel. The part of the brain the rod went through, predominantly the orbitofrontal and medial prefrontal cortices (Damasio, Grabowski, Frank, Galaburda, & Damasio, 1994), seemed critical to his temperament and decision-making. Though the story of Gage has evolved since then—he was able to hold down a job as a stagecoach driver later in life, so he may have recovered from some of his symptoms, and more recent analyses suggest that damage to white matter tracts as well as cortex contributed to his syndrome (Van Horn et al., 2012)—his case and similar ones have stimulated enduring interest in the ventromedial frontal lobes (VMF).

The VMF, as defined in this review, comprises the ventral portion of the frontal lobes, and includes both what the literature refers to as the ventromedial prefrontal cortex (VMPFC) and the orbitofrontal cortex (OFC). Both regions (which overlap in definition, see Anatomy section) have been implicated in diverse cognitive functions, such as memory and mental time travel, emotional experience, social cognition, and learning and decision-making (Lieberman, Straccia, Meyer, Du, & Tan, 2019; Roy, Shohamy, & Wager, 2012; Wilson, Takahashi, Schoenbaum, & Niv, 2014). These regions' role in such a diverse set of functions may be explained by their connectivity to other regions. The VMPFC and OFC are linked to structures involved in memory and emotion in the medial temporal lobe, project to regions involved in learning, like the ventral striatum, and receive inputs from many sensory processing areas.

Given the diverse functions in which this part of the brain has been implicated, a central question is whether we can ascribe any general function to the VMF as a whole. On the one hand, the VMF consists of two main cytoarchitectural networks, the central orbital network and the medial prefrontal network,

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with the first linked to sensory processing regions and the second linked to emotion and memory structures (Öngür & Price, 2000; Petrides & Pandya, 1994). On the other hand, these two networks are interconnected (Price, 2007), so different sub-regions of the VMF may work together to subserve a unified purpose. Several hypotheses for a unified theory of VMF function have been put forward, including the somatic marker (Damasio, 1994) and affective meaning hypotheses (Roy et al., 2012). Other recent accounts point to the VMF's role in learning the structure of the world, such as inferred relationships between entities, or beliefs about causes of events (Niv, 2019; Preston & Eichenbaum, 2013; Schlichting & Preston, 2015; Schoenbaum, Takahashi, Liu, & McDannald, 2011; Schuck, Wilson, & Niv, 2018; Wilson et al., 2014). This form of learning is referred to differently in different literatures, as a "cognitive map" or "state representation" or "schema". Importantly, a similar underlying cognitive process is implied by these different terms, even though the models may differ in the mechanistic details. Development of both schemas and state representations rely on an abstract representation of relationships extracted from individual elements, which can be generalized to new instances and allow for inference and prediction (Ghosh & Gilboa, 2014; Schuck et al., 2018; Wilson et al., 2014; Zeithamova, Dominick, & Preston, 2012).

To contribute to this emerging parsimonious view, we present a qualitative synthesis of human lesion studies of the VMF, based on a comprehensive review of published data spanning the last two decades. We chose to perform a systematic review to provide an unbiased view of the literature. We aim first to provide a more complete impression of the state of human lesion research concerning the VMF, and then to offer our perspective on how these findings from seemingly diverse domains can be understood in the context of schemas and state representations.

Methods

Anatomy

In this paper, we focus on lesions of the ventromedial frontal lobes (VMF), a term we use as a short-hand for lesions that include ventromedial prefrontal cortex (VMPFC) or orbitofrontal cortex (OFC). This includes damage to any portion of the orbitofrontal cortex (medial OFC: area 14; lateral OFC or ventrolateral PFC: area 12/47; central OFC: areas 11 and 13), the frontal pole (area 10), or anterior cingulate cortex (ACC; areas 24, 25, 32) below the genu of the corpus callosum (Petrides & Pandya, 1994). Some papers in this review differentiate lesions of OFC, which involve damage restricted to the ventral face of the prefrontal cortex, from lesions of VMPFC, which generally include some damage to both OFC as well as the medial wall below the genu of the corpus callosum. Other papers link particular deficits to damage to the lateral versus medial portions of the OFC, or focus specifically on the frontal pole. Figure 1 illustrates these regions, as they are commonly described in the literature (e.g., Stuss and Levine, 2002). Thus, in this paper, we use VMF to describe this general region, and "VMPFC" or "OFC" to refer to subregions within this area.

Literature search

The goal for this search was to include all papers between the years 1998 and August 2019 reporting studies of humans with permanent focal lesions to the VMF. We focused on group studies and excluded case studies because many of the functions tested, such social behaviours, personality and subjective decisions, have large natural variation in the general population. In these domains, groups studies are typically warranted to show a systematic difference between individuals with lesions to an area and control populations. We excluded damage due to neurodegenerative disease or traumatic brain injury because such lesions are diffuse and affect multiple brain systems, and thus it is difficult to conclude that a particular deficit is because of damage to a specific brain area. We did include penetrative brain injury because of its relatively more focal nature. Additionally, we excluded papers that did not have the VMPFC or OFC as a distinct region of interest either in design or analysis (except for voxel-based symptom-mapping analyses), as this review focuses on specific claims about the VMF. Finally, the date range was chosen to concentrate on more contemporary lesion studies. There were fewer papers prior to 1998 and many of these did not meet our inclusion criteria.

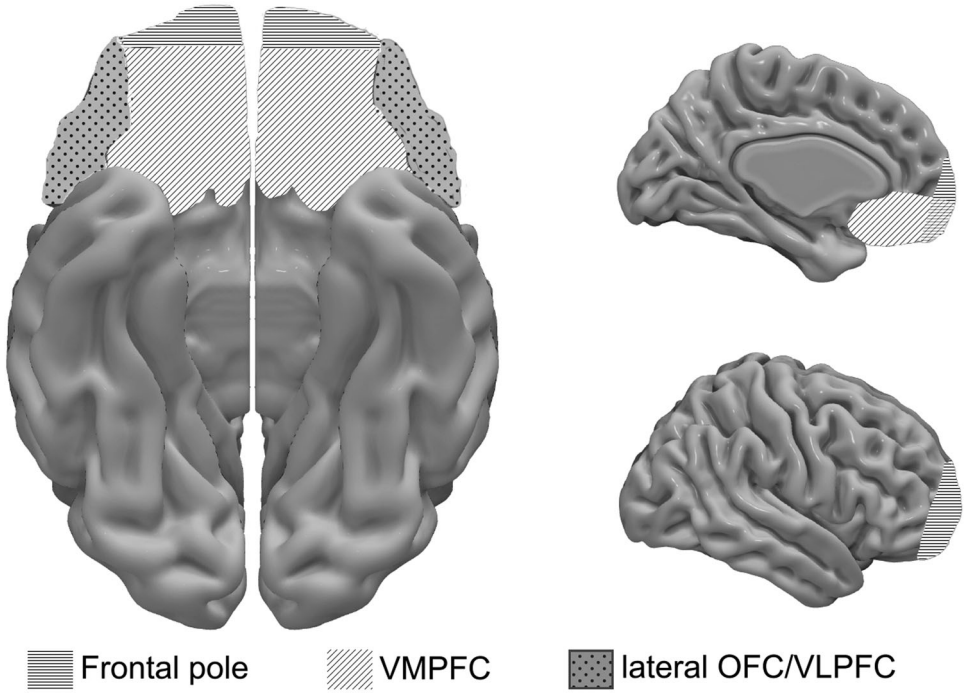

Figure 1. The patterned areas collectively denote what is considered the VMF in our review. The individual patterns denote its subregions, with boundaries following Stuss and Levine (2002) drawn on the ICBM 152 brain template. The diagonally shaded regions are considered VMPFC (includes medial OFC, central OFC, and ACC below the genu of the corpus callosum). The polka dotted regions are considered ventrolateral prefrontal cortex (VLPFC) or lateral OFC. The horizontally shaded region is frontal pole. As can be observed, the frontal pole and VMPFC overlap, and damage to frontal pole is commonly observed in lesion studies that investigate the VMPFC.

A search was performed in PsycINFO and in MEDLINE in August 2019, with search terms for "ventromedial prefrontal", "orbitofrontal", "medial prefrontal", and "ventral prefrontal" (and variations and acronyms of these words, such as "ventromedial PFC" or "VMPFC", see complete list in footnote[1]) AND ("lesion" OR "damage") with results limited to the English language, humans and the years from 1998 to 2019. The PsycINFO search yielded 2,355 results, and the MEDLINE search yielded 826 results. Further filters were applied to both searches to exclude neurological conditions (Alzheimer's, Parkinson's, epilepsy, multiple sclerosis, dementia), psychiatric disorders (schizophrenia, major depression, obsessive compulsive disorder), clinical case studies, and literature reviews (see complete list in footnote[2]), reducing the yield to 1,031 results from PsycINFO and 462 results from MEDLINE. 236 papers were duplicates between the two databases. The first author reviewed the titles and abstracts of the 1,257 unique papers and removed 1,011 papers not meeting criteria (e.g., reviews, case studies, non-lesion studies). Then, the first author reviewed the methods of the remaining 246 papers and excluded 74 papers where VMF was not a region of interest or where half or more (≥50%) of the subjects in the VMF group had damage due to traumatic brain injury (for the remaining papers, we describe how many of the group had TBI in Table 1). This process resulted in 172 papers meeting inclusion criteria.

Finally, we included 7 additional papers found by tracking citations from included papers and 5 additional papers known to the authors that were not recovered by any other search.

The final count of included papers is **184** (see Figure 2 for a summary of the process described above). Papers that grouped subjects by lesion location are listed in Table 1, and papers that grouped subjects by symptomology or used VLSM methods are listed in Table 2.

Structure of this paper

We review and synthesize the findings of these 184 papers below in separate sections according the major domains of function investigated: memory, executive function, emotion, social cognition, and valuation. As the scope of this review is expansive,

Table 1. List of reviewed papers that primarily group subjects by lesion location.

Study	Study type	Individuals with VMF damage	Etiology for VMF damage	Other frontal damaged individuals	Non-frontal damaged individuals	Non-brain damaged controls	Other functions assessed	Participant overlap
MEMORY								
Confabulation and Schemas								
Ciaramelli and Spaniol (2009)	behavioural	13 (6 confab, 7 non-confab)	ACoA rupture			13 HC		
Gilboa et al. (2009)	ERP	8	ACoA rupture			8 HC		
Turner et al. (2008)	behavioural	19 (11 orbital, 8 MF)	ACoA aneurysm, tumours (metastasis, meningioma, glioma, lymphoma), haematoma, abscess, AVM	16 (9 LL; 7 RL)	16 posterior patients	50 HC		
Kan et al. (2010)	behavioural	17 (10 confab, 7 non-confab)	ACoA aneurysm			20 HC		
Ghosh et al. (2014)	behavioural	10 (4 confab, 6 non-confab)	ACoA aneurysms			12 HC		
Spalding et al. (2015)	behavioural	6	resections, stroke, SAH			12 HC		
Wood et al. (2005)	behavioural	11	PBI, tumour resection, aneurysm, stroke, herpes encephalitis	8 (DL)		13 HC		
Spalding et al. (2018)	behavioural	6	resection, stroke, SAH			12 HC		
Koscik and Tranel (2012)	behavioural	15	tumor resection, cerebrovascular accident		36 BDC (17 MTL)	44 HC		
Warren et al. (2014)	behavioural	7	resections, stroke, SAH			14 HC		
Ciaramelli et al. (2009)	behavioural	10 (6 confab, 4 non-confab)	ACoA aneurysm			13 HC		
Duarte et al. (2010)	behavioural	7	ACoA, trauma, TBI (3)			14 HC (2 matched for each patient)		
Gilboa and Moscovitch (2017)	behavioural	same participants as Gilboa et al. (2009)						
Turner et al. (2007)	behavioural	11 OFC	ACoA aneurysm, meningioma, haematoma, absecess, AVM	8 MF, 8 LL, 7 RL		50 HC		
Autobiographical, prospection, mind-wandering and self-related processing								
Bertossi et al. (2016)	behavioural	7	ACoA aneurysm, TBI (1)		9 BDC			
Bertossi et al. (2016)	behavioural	7	ACoA aneurysm, TBI (2)			11 HC		
Kurczek et al. (2015)	behavioural	5	ACoA/SAH, meningioma resection		6 HIPP (bilateral)	11 HC		
De Luca et al. (2018)	behavioural	8	ACoA aneurysm		10 BDC (non-VMF or HIPP), 7 HIPP	10 HC		
Bertossi et al. (2017)	behavioural	6	ACoA aneurysm			11 HC	**working memory**	
Verfaellie et al. (2019)	behavioural	8	ACoA aneurysm		8 MTL	32 HC		
Bertossi and Ciaramelli (2016)	behavioural	7	ACoA aneurysm		11 BDC	20 HC		

Belfi et al. (2018)	behavioural	9	stroke, meniningioma resection			20 HC	
Philippi et al. (2012)	behavioural	6	N/A		8 BDC	15 HC	
Working memory							
Bechara et al. (1998)	behavioural	9	aneurysms	10 DL/M		21 HC	**IGT**
Barbey et al. (2011)	behavioural	24	PBI		40 non-OFC	54 HC	
Tsuchida and Fellows (2009)	behavioural, VLSM	7 OFC	surgical resection, stroke, aneurysm rupture	4 LL, 5 RL, 11 MF		29 HC	
Szatkowska et al. (2003)	behavioural	21 (12 resection of GR, 9 without resection)	ACoA rupture and GR resection			14 HC	
Szatkowska et al. (2011)	behavioural	19 (12 resection of GR, 7 without resection)	ACoA aneurysm and GR resection			10 HC	**valuation**
Kurczek and Duff (2012)	behavioural	6	meningioma, SAH, ACoA aneurysm			6 HC	
EXECUTIVE FUNCTION							
Cognitive control							
Szatkowska et al. (2000)	behavioural	12 (6 left VM, 6 right VM)	ACoA rupture, GR resection	6 right DL, 6 left DL		10 HC	
Funderud et al. (2013)	ERP	13	meningioma, TBI (3), glioma	11 LF		16 HC	
Keifer and Tranel (2013)	behavioural	13	stroke, aneurysm, menigioma, AVM, TBI (1)	14 DL	18 NF		
Løvstad et al. (2012)	behavioural	14	menigioma, TBI (4), glioma	10 LF		21 HC	
Solbakk et al. (2014)	ERP	12	meningioma, TBI (3), glioma			14 HC	
Maier et al. (2015)	ERP	7 ACC + VM	ACoA aneurysm		7 BDC (occipital, temporal, parietal)	7 HC	
Szatkowska et al.(2007)	behavioural	21 (12 with resection of GR, 9 without resection)	ACoA aneurysm (subset had resection of GR)			12 HC	
Tranel et al., 2008	behavioural	25	cerebrovascular disease, surgical resection, herpes simplex	37 DL, 18 DL + VM	25 BDC		
Reasoning							
Reverberi et al. (2005)	behavioural	24	arachnoid cyst, glioma, meningioma, stroke	11 LL, 11 RL		27 HC	
Reverberi et al. (2009)	behavioural	18	arachnoid cyst, glioma, meningioma, stroke	10 LL, 8 RL		25 HC	
Planning							
Peters et al. (2017)	behavioural	12	aneurysm rupture, tumor resection, stroke	11 FC		22 HC	
Tranel et al. (2007)	behavioural	9	cerebrovascular accident, tumour resection	8	17 NF	20 HC	
EMOTION							
Emotional experience							
Changes in affect/personality							
Anderson et al. (2006)	clinical scale, relative report	7 adult, 4 child-onset	NO ETIOLOGY for adults; for childhood (hemorrhage, tumour resection; skull fracture; cyst)	14 non-VM prefrontal	36 NF	none	

(*Continued*)

Table 1. Continued.

Study	Study type	Individuals with VMF damage	Etiology for VMF damage	Other frontal damaged individuals	Non-frontal damaged individuals	Non-brain damaged controls	Other functions assessed	Participant overlap
Barrash et al. (2000)	informant ratings	7	cerebrovascular accident, meningioma resection, anoxia, herpes encephalitis	14 non-VM prefrontal	36 NF	none		
Barrash et al. (2011)	relative report	28	none given	96 non-VM (frontal and non-frontal)		none		
Berlin et al. (2004)	behavioural	23	TBI (6), meningioma, ACoA aneurysm and SAH, epileptic focus, astrocytoma	20 non-OFC		39 HC	**reversal learning, future thinking**	
Berlin et al. (2005)	behavioural	23	same as Berlin et al. (2004)	20 non-OFC		39 HC; 19 borderline patients	**reversal learning, future thinking**	
Bramham et al. (2009)	self, informant report	20 OFC (6 OFC only, others with DM or lateral damage)	meningiomas, haematoma, ogliodendroma, cavernoma, astrocytoma, ACoA aneurysm, ependyoma	14 non-OFC (either DM or DL)		34 HC		
Lewis et al. (2015)	self report	62	PBI	129 other patients		none		
Pardini et al. (2010)	clinical scale, self report	17	PBI	51 DL	29 NF	37 controls		
Pardini et al. (2011)	relative report	56	PBI	51 LPFC	34 NF	29 HC		
Koenigs et al. (2008)	clinical interview, self report	20 (7 VHIS, 13 Iowa)	PBI (VHIS), tumor resection, AcoA aneurysm (Iowa)	5 DL/DM (VHIS)	101 NF (VHIS), 238 NF (Iowa)	52 HC (VHIS)		
Koenigs et al. (2008)	clinical interview	40	PBI		15 amygdala, 133 BDC (non-VMF or amygdala)	52 HC		
Hogeveen et al. (2017)	behavioural	23	PBI	20 DM	48 other	21HC	**choice consistency executive function, IGT**	
Abel et al. (2016)	clinical notes, neuropsych testing	23 (10 also studied pre-operatively)	meningioma resection	47 BDC (frontal/ temporal/ parietal/ occipital)				
Task related emotional changes								
Burin et al. (2014)	behavioural	7	ACoA aneurysm, subarachnoid hemorrhage, meningioma resction			7 HC		
Hilz et al. (2006)	behavioural	13	head injury (3), AVM, abscess, meningioma, surgery for epilepsy, stroke			13 HC		
Johnsen et al. (2009)	behavioural	10	ACoA rupture surgery, tumour resection		15 right somatosensory	20HC		
Jenkins et al. (2018)	behavioural	same participants as Jenkins et al. (2014)						
Motzkin et al. (2014)	fMRI	4	meningioma resection			19 HC		

Motzkin et al. (2015)	fMRI	4	meningioma resection			19 HC	
Motzkin et al. (2014)	fMRI	4	meningioma resection			19 HC	
Goel et al. (2017)	behavioural	17	pBI		24 parietal	22 HC	
Buchanan et al. (2010)	behavioural	18	meningioma resection, ACoA + SAH, infarct, trauama (2), subarachnoid cyst, AVM		12 BDC	54 HC	
Gillihan et al. (2011)	behavioural	7	ACoA rupture, stroke	8 LF		15 HC	
Emotion recognition							
Heberlein et al. (2008)	behavioural	7	ACoA aneurysm, bilateral ACA stroke	8 DL		16HC	
Wolf et al. (2014)	eye-tracking	3	meningioma resection		10 BDC (3 DM, temporal, cerebellar, lateral frontal + temporal)	21 HC	
Tsuchida and Fellows (2012)	behavioural, VLSM	10	ACoA rupture, tumor resection, stroke	10 DM, 9 LF		47 HC	
Wolf et al. (2016)	behavioural	7	meningioma resection, ACA aneurysm		4 BDC (temporal, occipital, 1 DM frontal)	25HC	
Jenkins et al. (2014)	behavioural	5 OFC, 7 VM (ACC + OFC)	surgical resections	4 ACC (dorsal), 11 DL		26 post-surgical patients (non-brain damaged)	**theory of mind**
Hornak et al. (2003)	behavioural, self-report	24	surgical resection (epilepsy, tumour, AVM)	11 DL		48 HC (voice experiment), 25 (face exp)	**emotional experience**
Willis et al. (2014)	behavioural	7	head injury (3), stroke, abscess, meningioma	6 non-OFC		61HC (task 1/2), 49HC (subset task 3/4)	
Shaw et al. (2005)	behavioural	14	same as Hornak et al. (2003)	17 DL	54 Temporal Lobe patients	91 HC	
Vaidya and Fellows (2019)	behavioural	17	tumor resection, aneurysm rupture	20 FC		27 HC	
SOCIAL COGNITION							
Social perception							
Xia et al. (2015)	behavioural	13 VMF (7 LOFC group)	aneurysm, tumour resection, stroke	12 non-VMF (18 non-LOFC)		53 HC	
Karafin et al. (2004)	behavioural	15	None given		11 BDC	32 HC	
Leland and Grafman (2005)	behavioural	17	None given			27 HC	**future thinking, risk taking**
Mah et al. (2004)	behavioural	12 OFC, 5 OFC+ACC, 5 OFC + ACC + DLPFC	PBI, tumor resection, SAH	4 DL only		31 HC	
Mah et al. (2005)	behavioural	20	PBI, 1 tumour	9 DL		23 HC	
	behavioural	14	none given	13 DL, 14 DM		22 HC	

(*Continued*)

Table 1. Continued.

Study	Study type	Individuals with VMF damage	Etiology for VMF damage	Other frontal damaged individuals	Non-frontal damaged individuals	Non-brain damaged controls	Other functions assessed	Participant overlap
Pullen et al. (2006)								
Zacks et al. (2016)	behavioural	16 (2 VMPFC only, 13 VMPFC +DLPFC, 1 VMPFC + DLPFC + RSP)– used regional regression analysis	PBI	24 DL (8 DL only, 13 VMF + DL, 2 DL + RSP)	13 RSP (10 RSP only, 1 VMF+ DL + RSP, 2 RSP + DL), 80 other lesions	34 HC		
Emotional and cognitive empathy								
Leopold et al. (2012)	behavioural	30	PBI		76 posterior group	55 HC		
Gupta et al. (2012)	behavioural	7	meningioma, SAH/ACoA			7 HC		overlap with Young et al. (2010) and Koenigs and Tranel (2008)
Stolk et al. (2015)	behavioural, VLSM	8	ACoA rupture		6 BDC (occipital, temporal, parietal)	15 HC		
Gordon et al. (2014)	behavioural	7	same as Barrash et al. (2000)		4 HIPP	7 HC		
Lee et al. (2010)	behavioural	12						
Moral judgment								
Koenigs et al. (2007)	behavioural	6	ACoA aneurysm, meningioma resection			12 HC		
Ciaramelli et al. (2007)	behavioural	7	ACoA rupture			12HC		
Moretto et al. (2010)	behavioural	8	ACoA rupture		7 non-frontal (spared amygdala/insula)	18 HC		
Taber-Thomas et al. (2014)	behavioural	9 developmental	trauma (3), resection	6 adult-onset VM (from Koenigs et al., 2007)		12 HC (from Koenigs et al., 2007)		
Thomas et al. (2011)	behavioural	9	ACoA aneurysm, subarachnoid hemorrhage (SAH), meningioma resection		9 non-limbic damaged patients	11 HC		
Young et al. (2010)	behavioural	9	meningioma resection, head trauma (1), SAH + ACoA aneurysm		7 BDC (non limbic)	8 HC		
Croft et al. (2010)	behavioural	4	cerebrovascular accident, tumor resection		4 HIPP, 6 BDC	10 HC		
Ciaramelli et al. (2012)	behavioural	8	ACoA rupture, TBI (3)		9 BDC (non-amygdala)	20 HC		
Ciaramelli et al. (2013)	behavioural	20	ACoA rupture, TBI (3), tumor resection		12 BDC (non-amygdala)	24 HC		
Social attitudes								
Milne and Grafman (2001)	behavioural	7	PBI	3DL		15 HC		
Gozzi et al. (2009)	behavioural	18 VM, 15 VL	PBI		10 anterior temporal	43 HC		
Asp et al. (2012)	scale	10	stroke, tumor resection		10 BDC (non-limbic)	16 medical comparison (non-neurological)		

Forbes et al. (2011)		30 (incl.with additional DL damage)	PBI			52 HC
Zhong et al. (2017)	scale	24		31 DL	37 NF	30 HC
Stolk et al. (2015)	behavioural	8	ACoA rupture		6 NF	15 HC
Cristofori et al. (2016)	behavioural, VLSM	19	PBI	14 DL	13 iPTC, 30 other lesions	33 HC
Social decision-making						
Koenigs and Tranel (2007)	behavioural	7	meningioma resection, ACoA aneurysm leading to subarachnoid hemorrhage		14 non-VMPFC	14 HC
Krajbich et al. (2009)	behavioural	6	None given (assume similar to Koenigs)		20 BDC	16HC
Moretti et al. (2009)	behavioural	7	ACoA rupture		6 NF	14HC
Gu et al. (2015)	behavioural	6	removal of gliomas	6 insula	6 patients outside vmpfC/insula	40HC
Wills et al. (2018)	behavioural	8 VMF + DL (used regional regression analysis)	epilepsy, TBI (1), meningioma, oligodendroglioma, focal cortical dysplasia, haematoma			29 HC
Chen et al. (2015)	behavioural	11	tumour resection, stroke		12 BDC	14 HC
Moretto et al. (2013)	behavioural	10	resection of tumors		10 NF	10 HC
VALUATION Learning						
Iowa Gambling Task (IGT)						
Sanfey et al. (2003)	behavioural	9	PBI	4 FC		17 age-matched controls, 63 undergraduates
Waters-Wood et al. (2012)	behavioural	10	meningioma, ACOA aneurysm, cyst, pituitary tumour			30 HC
Ouerchefani et al. (2017)	behavioural	10 VM, 8 DL + VM	oligoastrocytoma, haemorrhagic contusion (4/10 in VM group, 1/8 in VM + DL group)			34 HC
Xiao et al. (2013)	behavioural	13				64 HC (not age or education matched)
Discriminative learning						
Chase et al. (2008)	behavioural	14	tumour, aneurysm, infarct, haemorrhage	22 non-OFC (both frontal and other damage)		35 HC
Wheeler and Fellows (2008)	behavioural	9	ACoA aneurysm rupture, stroke, tumour resection	11 DL		24HC
Vaidya and Fellows (2016)	behavioural, VLSM	17	tumor resection, hemorraghic and ischemic stroke, aneurysm	10 DM, 7 LL, 6 RL		21 HC
Reversal Learning						
Fellows and Farah (2003)	behavioural	8	ACoA rupture, ACA stroke	12 DL		12 HC

(*Continued*)

Table 1. Continued.

Study	Study type	Individuals with VMF damage	Etiology for VMF damage	Other frontal damaged individuals	Non-frontal damaged individuals	Non-brain damaged controls	Other functions assessed	Participant overlap
Hornak et al. (2004)	behavioural	11 bilateral OFC/MF	TBI (2), meningioma, ACoA + SAH	3 medial only, 5 DL, 6 DL+DM. 6 DL +DM + OFC		25HC		
Fellows and Farah (2005a)	behavioural	9	ACoA rupture, ACA infarct	11 DL		17 HC, 14 HC on IGT only		
Tsuchida et al. (2010)	behavioural, VLSM	11	aneurysm rupture, tumor resection, stroke	12 LF, 13 MF		48 HC		
Kumaran et al. (2015)	behavioural	11	meningioma, AVM, SAH, stroke		11BDC	11HC		
Camille, Tsuchida et al. (2011)	behavioural	5 OFC	stroke, tumour resection, aneurysm	4 dorsal ACC		17 HC		
Nahum et al. (2009)	behavioural	14 with OFC damage	ACoA aneurysm, TBI (6/14)		17 amnesics (6 overlap with OFC group)	12 HC		
Contingency learning								
Hochman et al. (2010)	behavioural	14	subset of VMF participants from Bechara et al. (2000); no HC				**IGT**	
Kovach et al. (2012)	behavioural	8 frontal pole	surgical resection, aneurysm, stroke, abscess		8 BDC (7 temporal, 2 extend to operculum)	14 HC		
Noonan et al. (2017)	behavioural	11 (5 medial OFC, 5 lateral OFC, 1 both)	tumor resection, ischemic stroke, hemorrhage	6 DM		22 HC		
O'Callaghan et al. (2019)	behavioural	8	meningioma resection, ACoA aneurysm, SAH	7 LF		17 HC		
Devaluation								
Reber et al. (2017)	behavioural	6	meningioma resection, stroke		7 BDC (2 frontal, temporal, occipital)	20 HC		
Decision *Future Thinking*								
Bechara et al. (2000)	behavioural	8	meningioma resection, stroke			17 HC	**IGT**	
Fellows and Farah (2005b)	behavioural	12	ACoA rupture, stroke	13 DL	13 NF	26HC		
Sellitto et al. (2010)	behavioural	7	ACoA rupture, TBI (2)		9 NF	20 HC		
Risk and uncertainty								
Clark et al. (2008)	behavioural	20	ACoA rupture–SAH, tumour resections	14 insula, 12 DL		41 HC		
Clark et al. (2014)	behavioural	17	ACoA rupture, tumour resections	8 insula	6 amygdala	16HC		
Hsu et al. (2005)	behavioural	5	meningioma resection		7 temporal lobe	none		
Manes et al. (2002)	behavioural	5 restricted to OFC	hemorrhage, meningioma, ogliodendroma	4DL, 5DM, 5 Large		13 HC		
Roger et al (1999)	behavioural	10	surgery for epilepsy or tumour, stroke	10 DL/M		26 HC		
Studer et al. (2015)	behavioural	13	hemorrhage, tumour resection		13 post parietal	22 HC		

Weller et al. (2007)	behavioural	7	None given		16 amygdala	30 HC
Pujara et al. (2015)	behavioural	5	meningioma resection	2 dorsal frontal	3 lateral temporal	30 HC
Spaniol et al. (2019)	behavioural	6	ACoA rupture		6 BDC	30 HC
Regret						
Camille et al. (2004)	behavioural	5	aneurysm, infarct, head injury (1)	3		18 HC
Larquet et al. (2010)	behavioural	10	mengioma, angioma, TBI (2), tumours			20 HC, 21 SZ
Levens et al. (2014)	behavioural	7 VM, 6 VL	ACoA aneurysm or tumour resection		5 NF	26HC
Choice consistency						
Fellows and Farah (2007)	behavioural	10	ACoA aneurysm rupture, stroke	11 DL		19 HC
Henri-Bhargava et al. (2012)	behavioural	15	stroke, aneurysm rupture, tumour resection	8 non-VM frontal		23 HC
Camille, Griffith, et al. (2011)	behavioural	9	ACoA aneurysm rupture, stroke			22HC
Bowren et al. (2018)	behavioural	16			16 BDC	16 HC
Decision confidence						
Scherer et al. (2015)	behavioural	9			10 BDC	15 HC
Gomez-Beldarrain et al. (2004)	behavioural	14	hemorrhage, infarct, surgery for mengioma, trauma (6/14)	6 DL	9 parietal	20 HC
Decision processes						
Fellows, 2006	behavioural	13	ACoA rupture, stroke	11 DL		21 HC
Vaidya et al. (2017)	behavioural, VLSM	13		20 FC		27 HC
Schnyer et al. (2009)	behavioural	8–9 with damage in VM	stroke, aneurysm, 1 contusion patient (right ventral frontal)	6		11 HC
Pelletier and Fellows (2019)	behavioural	12		12 FC		24 HC
Vaidya and Fellows (2015a)	behavioural, VLSM	13	tumour resection, aneurysm rupture, stroke	8 LF, 12 DMF		27 HC
Reward and attention						
Pujara et al. (2016)	fMRI	5	meningioma resection			17 HC
Vaidya and Fellows (2015b)	behavioural	9	tumour, aneurysm, stroke	7 LF, 11 DM		21 HC
Manohar and Husain (2016)	behavioural	19 MF (13 VM)	ACA ruptures	8 DL		34 HC

(*Continued*)

Table 1. Continued.

Study	Study type	Individuals with VMF damage	Etiology for VMF damage	Other frontal damaged individuals	Non-frontal damaged individuals	Non-brain damaged controls	Other functions assessed	Participant overlap
Koenigs and Tranel (2008)	behavioural	12	meningioma, ACoA aneurysm–SAH, trauma (2)		16 BDC	16 HC		10 of the VMPFC overlap with Anderson et al. (2006); Koenigs and Tranel (2008); Koenigs et al. (2007)
Aridan et al. (2019)	11		stroke, tumor, aneurysm rupture			30 HC		

Notes: 1. AVM = arteriovenous malformation; ACoA = anterior communicating artery; SAH = subarachnoid hemorrhage; PBI = penetrative brain injury; TBI = traumatic brain injury (number included are noted in brackets); confab = confabulating; FC = frontal controls (frontal damage not incl. VMF); GR = gyrus rectus; DL = dorsolateral prefrontal; DM = dorsomedial prefrontal; ACC = anterior cingulate cortex; MF = medial frontal; VM = ventromedial frontal; VL = ventrolateral; OFC = orbitofrontal cortex; LF = lateral frontal; LL = left lateral frontal; RL = right lateral frontal; NF = non-frontal; MTL = medial temporal lobe; HIPP = hippocampal damaged; HC = healthy control (age matched unless otherwise specified); BDC = brain damaged controls (may include some frontal patients as part of this group, noted in brackets where specified); RSP = right superior posterior cortex; iPTC = inferior posterior temporal cortex; VHIS = Vietnam Head Injury Study. 2. If the study has the all the same participants as another paper, it will say "participants from XXX". If the VMF group is the same as another study (but with different comparison groups), it will be noted in the etiology section. If there is overlap in participants between one paper and another, it will be noted in the "overlap" section. Overlaps are noted for the paper where the authors mention it (thus if paper A and paper B share patients but only paper B mention it, the note will appear for paper B in this table). 3. The studies are categorized by domain of where deemed most appropriate by this review, which may be different than the authors' own characterization in that study. Any other functions they investigate are in the "Other functions assessed" column. 4. a study may have additional participants in a separate fMRI portion or younger comparison group; they are not included in this table if they are not compared to the lesion groups.

we have structured the paper so as to accommodate both readers interested in a basic overview of the findings for each domain and readers interested in the granular details within each domain. In each section, we start off with an executive summary of the findings in the domain, noting whether such findings are consistent or mixed. Within the body of each section, we elaborate in more detail the studies on which these conclusions are based. We then end each section with a statement on whether there are any sub-regional specificities to the functions discussed. Finally, in the General Discussion, we discuss the implications of the findings across domains for a parsimonious account of the VMF.

Memory

Executive summary

The VMF has extensive connections to medial temporal lobe (MTL) structures, such as the hippocampus and perirhinal and entorhinal cortices. The VMF causes some of the same deficits as MTL damage to autobiographical memory, future-thinking and scene construction (see review by McCormick, Ciaramelli, De Luca, & Maguire, 2018). Individuals with VMF damage also retain preserved levels of semantic knowledge, though the accuracy of semantic details are somewhat impaired. However, the impairments are to different extents, and for different reasons, than they are with damage to the MTL. For instance, findings are mixed as to whether individuals with VMF damage produce less vivid episodic details about memories and projections of the future, which may depend on the manner in which they are solicited. Individuals with VMF damage also exhibit unique memory impairments that are not typically observed after MTL damage, such as confabulation and a reduced benefit for remembering or generating information regarding the self. Investigations of confabulation after VMF damage have led to theories that the VMF's role in memory is to monitor memory traces and maintain the integrity of the present schema or context. Paradoxically, while individuals with VMF damage increasingly rely on semantic gist in place of episodic details when retrieving memories, they are also impaired in placing memories in their proper schematic frameworks or benefitting from recalling items that fit the right schema. In particular,

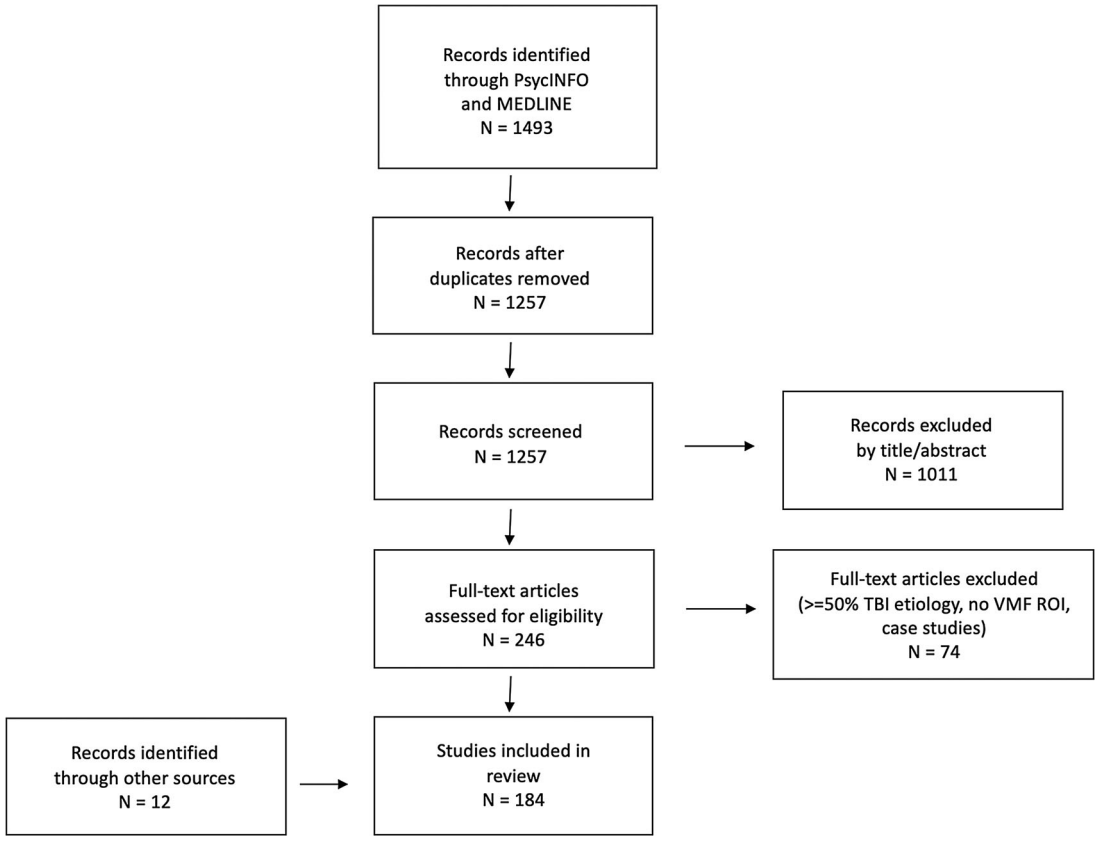

Figure 2. The identification and screening process for the systematic review.

impairments to the schema of the self as an organizing framework lead to a decreased benefit for recalling self-related memories. Finally, while VMF damage causes some impairments in working memory, these deficits are not specific to VMF and instead are observed generally after prefrontal damage.

Confabulation and schemas

Confabulation

Confabulation, or unintentional distortions of memory, is consistently observed in a subset of individuals with damage to the VMF, often through the rupture of the anterior communicating artery (ACoA). Confabulating individuals have beliefs and memories that they are unaware of as being false, a condition often referred to as "honest lying" (Moscovitch, 1989). Accounts suggest that confabulators have strategic memory retrieval failure (Gilboa et al., 2006; Hebscher & Gilboa, 2016). In these models, other parts of the prefrontal cortex initiate memory search and generate retrieval cues, and the VMF monitors the accuracy of the memory trace (Hebscher & Gilboa, 2016).

Many studies of confabulation compare individuals who confabulate to those who do not, in both anatomical and functional terms (Ciaramelli & Spaniol, 2009; Ghosh, Moscovitch, Colella, & Gilboa, 2014; Gilboa et al., 2006; Kan, Larocque, Lafleche, Coslett, & Verfaellie, 2010; Schnider & Ptak, 1999; Turner, Cipolotti, Yousry, & Shallice, 2008). Anatomically, the lesions of those with confabulation symptoms overlap in the medial OFC and basal forebrain (Hebscher, Barkan-Abramski, Goldsmith, Aharon-Peretz, & Gilboa, 2016; Schnider & Ptak, 1999; Turner et al., 2008).

One of the distinctions between confabulators and non-confabulators is that confabulators seem to confuse highly implausible, semantically unrelated details for reality. For example, for the biblical story of Noah's Ark, while even healthy controls might falsely endorse "Moses" as the animal conveyor (even though they possess the correct knowledge), only confabulators endorse "Malcolm X" as the person who brought the animals onto the Ark (Kan et al., 2010). Similarly, confabulators were uniquely susceptible to incorporating unlikely idiosyncratic details while retelling familiar stories, such as fairy tales, and were more likely to endorse implausible lures (things that had

Table 2. List of reviewed papers that primarily use voxel-lesion symptom mapping, or other lesion-symptom correlation methods.

Study	Study type	Number of total individuals with lesion	Number in frontal lobe	Comparison groups	Etiology
Memory					
Hebscher et al. (2016)	VLSM	27	27	19 HC	stroke, tumour resections, TBI (1), encephalitis
Schnider and Ptak (1999)	lesion symptom overlap	18 (6 confab, 12 non-confab amnesic)		10 HC	ACoA rupture, herpes encephalitis, hypothalamic granuloma, macroadenoma of pituitary gland
Gilboa et al. (2006)	lesion symptom overlap	12 (4 confab, 8 non-confab)	12	16 HC, 4 MTL	ACoA rupture (frontal)
Schnyer et al. (2004)	lesion symptom overlap	14	14	18 HC	stroke, aneurysm, TBI (4)
Philippi et al. (2015)	VLSM	92		34 HC	hemorrhage, infarct, surgical resections
Executive Function					
Tsuchida and Fellows (2013)	VLSM	28	28	50 HC	stroke, tumour resection, aneurysm
Volle et al. (2011)	VLSM	45	19	110 HC	hemorrhage, brain tumour, stroke
Cipolotti et al. (2016)	VLSM	165	165	60 HC	stroke, tumour, meningioma
Arbula et al. (2017)	VLSM	37	21	41 HC	meningioma, glioma
Chapados and Petrides (2013)	VLSM	45	25	25 HC	surgical removal (epilepsy, tumor), cerebrovascular accident
Aron et al. (2003)	lesion symptom overlap	37	37	18 HD, 19 HC	ACoA aneurysm, tumors, infarct, surgery for cyst, infarct, SAH, hemorrhage, AVM
Aron et al. (2004)	lesion symptom overlap	36	36	20 HC	same patients as Aron et al. (2003)
Emotion					
Dal Monte et al. (2013)	VLSM	180		53 HC	PBI
Eimontaite et al. (2018)	VLSM	92		23 HC	PBI
Operskalski et al. (2015)	VLSM	130		none	PBI
Calamia et al. (2018)	VLSM	232		none	ischemic and hemorraghic stroke, AVM, tumour resection, resection for epilepsy (temporal lobe), aneurysm, encephalitis, head trauma (5)
Campanella et al. (2014)	VLSM	71	31	none	glioma, meningioma, metastasis
Falquez et al. (2014)	VLSM	27		23 HC	tumours and resection of tumours
Pardini et al. (2011)	lesion symptom overlap	155	106	42 HC	PBI
Social					
Cristofori et al. (2015)	VLSM	102	36	31 HC	PBI
Driscoll et al. (2012)	VLSM	192	unspecified	54 HC	PBI
Robinson et al. (2014)	VLSM	62	37		SAH, surgical resection, encephalitis, TBI (3), intracerebral hemorrhage
Glass et al. (2015)	VLSM	114		32 HC	PBI
Channon et al. (2010)	lesion symptom overlap	29	18		glioma, meningioma, metastasis, absecess, cyst
Channon et al. (2007)	lesion symptom overlap	45	23	26 HC	lymphoma, glioma, meningioma, haemangioma, metastasis
Nakajima et al. (2018)	VLSM	20	20	18 HC	tumour resection
Valuation					
Glascher et al. (2012)	VLSM	344	165	none	stroke, tumour resection, temporal lobotectomy, encephalitis, other focal pathology

Notes: HC = healthy controls; MTL = medial temporal lobe; HD = Huntington's Disease; VLSM = voxel-lesion symptom mapping. Lesion symptom overlap = studies that used symptomology to derive lesion overlap maps.

never happened to them) as true of their autobiographical experience. (Gilboa et al., 2006).

At the same time, there is an underlying memory deficit common to VMF damage, as both confabulators and non-confabulators exhibit contextual confusion in memory retrieval (Gilboa et al., 2006), but see (Schnider & Ptak, 1999). Both confabulators and non-confabulators with VMF damage made more perceptual context errors, mistaking whether an item had been presented as a picture or as a word (Ciaramelli & Spaniol, 2009). Individuals with damage to the OFC (who were not examined for confabulation), an area that was associated with successful retrieval of temporal and spatial context in an fMRI study of healthy participants, were worse than matched healthy controls at identifying the temporal context (i.e., which task block) of a studied object (Duarte, Henson, Knight, Emery, & Graham, 2010). In a related finding, individuals with orbital damage offered more extra-list intrusions (i.e., words not from the studied lists) after being prompted with the category of words they had forgotten (Turner, Cipolotti, Yousry, & Shallice, 2007).

Familiarity

In accordance with the theory that an intact VMF monitors memory traces, several studies have found that damage to the VMF reduces feelings of familiarity. Damage to ventromedial areas was associated with less accurate feeling of knowing decisions (where participants had to predict whether they would recognize the answer if they saw it among alternatives) (Schnyer et al., 2004). An ERP study of individuals with VMF damage (some of whom were either actively confabulating or had a history of confabulation) found they had a reduced neural signature to familiar faces (Gilboa, Alain, He, Stuss, & Moscovitch, 2009), which was preceded by a decrease in coherence between frontal and temporal regions (Gilboa & Moscovitch, 2017).

Schemas

The investigation of why confabulation happens has led to work on a more general theory of VMF's involvement in schema construction. Schemas are associative networks that are abstracted out of multiple episodes of experience, lack unit detail, and are adaptable to new situations (Ghosh & Gilboa, 2014). Some confabulation symptoms may be explained by a weakening of such schematic representations.

Several studies have supported the view that VMF damage causes confusion between different schemas. Ghosh et al. (2014) presented participants with a task that first queried a given word's relation to one schema (e.g., "going to bed"), and then to a second, different schema (e.g., "visiting the doctor") ten minutes later. Confabulators were impaired in correctly linking a word to its relevant schema compared to individuals with VMF damage who did not confabulate. Relatedly, individuals with right orbitofrontal damage made more errors linking components of a social script (e.g., "read the menu") to their relevant event ("going to dinner") (Wood, Tierney, Bidwell, & Grafman, 2005). Finally, in another study, participants were asked to make a moral judgement of a word (either a morally wrong one, like "murder", a non-moral negative one, like "cancer", or a neutral one, like "baking"), which followed a distractor word of one of the same three categories. Subjects with VMF lesions showed a stronger tendency to make incorrect judgments after a morally wrong distractor, but not after non-moral negative distractors, consistent with schema intrusion from the moral category when the distracter is incongruent with the target word (Cameron, Reber, Spring, & Tranel, 2018).

In addition to confusing schemas with each other, individuals with VMF damage also had weakened schematic benefit on memory. Spalding, Jones, Duff, Tranel, and Warren (2015) tested individuals with VMF damage and controls in a task where pictures and words were presented that were either schema-congruent (e.g., pizza and oven) or incongruent (cactus and ice rink). In a subsequent recognition phase, controls were more likely to identify items that they had seen before in the schema-congruent condition, indicating that the schema had helped their learning. Individuals with bilateral VMF lesions (with overlap in the subgenual ACC, area 14, 25, and inferior 24) failed to show this schematic benefit, instead showing the same recall performance in both the congruent and incongruent conditions.

Schema-like associates

In addition to research on schemas, there are also studies showing that VMF damage impairs schema-like mechanisms, such as the recall of semantically associated words and associative inference. These simpler associative networks between individual elements are the building blocks of schemas. In the

Deese-Roediger-McDermott (DRM) paradigm, participants study a list of semantically associated words like "snow" and "cold", and then are asked at test whether they saw an unstudied but related word like "winter" (known as critical lures). This paradigm aims to elicit a pattern completion process that induces the false endorsement of the critical lure. Control participants are more likely to report having previously encountered the critical lures, but individuals with VMF damage had reduced false alarms for critical lures, suggesting that their semantic network is weakened (Ciaramelli, Ghetti, & Borsotti, 2009; Warren, Jones, Duff, & Tranel, 2014). Instead, confabulators were more likely to false alarm to unrelated lures (unstudied, not semantically related words, e.g., "lion"). Interestingly, adding a distractor task (counting) during the DRM paradigm reduced false recall of unrelated lures in confabulators, while the recall of critical lures was unchanged (Ciaramelli et al., 2009).

Similar to semantic associations, the abilities to extract relationships and draw inferences are critical aspects of schema formation. VMF damage impairs these kinds of inferences. In a recent study, Spalding et al. (2018) presented subjects with pairs of objects, structured as "AB" pairs and "BC" pairs. Critically, objects A and C are linked through the overlapping item B but are never presented together. Participants had to recall both direct associations ("AB" and "BC") and the inferred association that was never shown ("AC" pair). The VMF group performed comparably to healthy controls in recall for the direct associations (though showing some memory decline in a second test), but were worse at identifying the inferred AC pair. In a different task, in which participants received feedback regarding pairs of stimuli (i.e., A is more correct than B, B is more correct than C), Koscik and Tranel (2012) found that individuals with VMF damage could acquire the initial paired relationships, but were impaired in making choices that depended on transitive inference.

Autobiographical memory, prospection, mind-wandering, and self-related processing

Autobiographical memory

Autobiographical memories involve both external or semantic elements (information such as addresses), and internal or episodic elements (that is, elements pertaining to a specific time and place, with vivid, experienced details). A whole brain VLSM study found that damage to parts of the default mode network (DMN), including the mPFC, posterior cingulate cortex (PCC), and MTL, is associated with lower scores on both semantic and episodic autobiographic memory (Philippi, Tranel, Duff, & Rudrauf, 2015).

However, other studies suggest that task differences can impact the degree to which VMF damage affects semantic or episodic details in autobiographical memory., In the VLSM study that found VMF involvement, Philippi et al. (2015) assessed semantic details by asking autobiographical questions (e.g., "What is the name of your high school") and marking the answers correct or incorrect based on information from a family member or close friend. In tasks that prompt a story-like memory recall with cue words, individuals with VMF damage do not differ in the number of semantic details they produce for past memories (Belfi, Karlan, & Tranel, 2018; Bertossi, Tesini, Cappelli, & Ciaramelli, 2016), but do generate more inaccurate details (regardless of confabulation status; Bertossi, Tesini, et al., 2016).

However, there is mixed evidence for the degree to which VMF damage impairs internal details, which may differ across types of memory and manners in which memory is elicited. Two studies using prompts to elicit recounting of memories found a reduction in internal details for individuals with VMF damage compared to healthy controls (Bertossi et al., 2016; Philippi et al., 2015), while a third did not (Kurczek et al., 2015). It has been hypothesized that the disparity in findings is because the VMF is necessary for elaboration of extended scenes—Kurczek et al. (2015) required recall of memory only for a moment in time, while Bertossi, Tesini et al. (2016) required recall of a more extended event (McCormick et al., 2018). In another study using familiar music and famous faces as prompts for episodic memory, Belfi et al. (2018) found that individuals with VMF damage gave fewer internal details for memories prompted by listening to the music, but not for memories prompted by the famous faces.

Prospection

Impairments in constructing vivid episodic detail after VMF damage go beyond retrospective memory and extend to the construction of imagined scenes. Just like individuals with damage to the medial temporal

lobes (MTL) who are impaired in constructing future or fictional episodes (Hassabis, Kumaran, Vann, & Maguire, 2007; Race, Keane, & Verfaellie, 2011), individuals with damage to the VMF include fewer episodic details when imagining future or fictional scenes (Bertossi, Aleo, Braghittoni, & Ciaramelli, 2016; Bertossi, Candela, De Luca, & Ciaramelli, 2017; Bertossi, Tesini, et al., 2016; Verfaellie, Wank, Reid, Race, & Keane, 2019). Interestingly, like individuals with damage to the hippocampus, individuals with VMF damage are also impaired at being able to visualize the extension of a scene outside the boundaries of a picture (De Luca et al., 2018). These studies illustrate that, as with MTL structures, the VMF is a critical substrate for constructing imagined details.

Mind-wandering

Trouble constructing past or future scenes could also impact mind-wandering. One study found that individuals with VMF damage both engage in less mind-wandering compared to healthy and brain-damaged controls, and when their minds do wander, they think less about the future and the past (Bertossi & Ciaramelli, 2016). Interestingly, these individuals also reported less day-dreaming in a questionnaire. While more studies are needed to investigate the role of the VMF in mind-wandering, this result fits with the general pattern of individuals with VMF damage being impaired in autobiographical constructions of the past and future.

Self-related processing

As the "self" constitutes an organizing schema by which memories relevant to one's identity are processed (Conway, 2005), it has been suggested that the disruption of schematic memory after VMF damage would impair self-related memory processing as well (Verfaellie et al., 2019). Evidence on whether VMF damage affects references to the self in memories is mixed. Using a narrative construction task, Kurczek et al. reported fewer references to the self, whereas Bertossi et al. finding greater references to the self (Bertossi, Tesini, et al., 2016; Kurczek et al., 2015). Verfaellie et al. (2019) found that individuals with VMF damage did not produce more episodic details for a future scenario involving the self than one involving another person, in contrast to healthy controls who demonstrated a greater number of self-references. Individuals with VMF damage also produced fewer episodic details overall. Notably, although individuals with MTL damage also produced fewer episodic details, they still showed the self-referential effect. Philippi, Duff, Denburg, Tranel, and Rudrauf (2012) similarly found that individuals with VMF damage did not recall traits that were processed for the self ("does this trait describe you?") better than those that were processed for another person ("does this trait describe Oprah"). In sum, VMF damage, unlike MTL damage, uniquely impacts the advantage for memories that are organized around the self.

Working memory

There is some evidence that working memory may be impaired after VMF damage, for both words and visual images (Bechara, Damasio, Tranel, & Anderson, 1998; Bertossi et al., 2017; Szatkowska, Grabowska, & Szymanska, 2001; Szatkowska, Grabowska, & Szymańska, 2003). However, while damage within the VMF may be associated with errors in working memory, especially under more difficult conditions (Barbey, Koenigs, & Grafman, 2011; Szatkowska, Szymańska, Marchewka, Soluch, & Rymarczyk, 2011), VLSM analyses have linked working memory performance more specifically with dorsomedial and lateral frontal damage (Robinson, Calamia, Gäscher, Bruss, & Tranel, 2014; Tsuchida & Fellows, 2009).

One interesting aspect of working memory is the ability to maintain a cohesive narrative in conversation. Smoothly-flowing conversation uses signifiers that refers to a previous sentence, or cohesive ties (e.g., using a pronoun to stand for a name that has already been said previously, or words like "but" to relate a sentiment to the previous one), and maintains a coherent global topic. Individuals with hippocampal amnesia produce less cohesive ties (Kurczek & Duff, 2011), raising the question of whether VMF damage would produce a similar effect. However, individuals with VMF damage did not exhibit a difference in the number of cohesive ties and topic maintenance compared to healthy controls (Kurczek & Duff, 2012). Thus, despite the similarity of VMF damage to hippocampal damage in some aspects of memory functioning, VMF does not appear necessary for executive maintenance of a coherent conversation.

Anatomical specificity

For the deficits discussed above, there is not much evidence regarding anatomical specialization within the VMF. For autobiographical memory, widespread areas with the VMF, along with other regions of the DMN, appear to be important (Philippi et al., 2015). For memory impairments, the relative importance of the medial OFC versus the nearby cholinergic basal forebrain has been widely debated. It has been proposed that damage to the basal forebrain causes amnesic symptoms, whereas damage to the medial OFC causes lasting confabulatory symptoms, and that the medial OFC is therefore necessary for accurate contextual placement of memory (Hebscher et al., 2016; Turner et al., 2008).

Executive function

Executive summary

Damage to the VMF does not impact performance on most classic neuropsychological tests of executive function, such as IQ, verbal fluency, attention or set shifting, and response inhibition. The deficits that are observed after VMF damage in some other executive function tasks are not specific to the VMF, since they are also found in individuals with damage to other prefrontal areas. Reasoning (*i.e.*, induction of abstract rules and logical deduction), planning and real-life problem solving are also sensitive to damage throughout the prefrontal cortex, including VMF. However, VMF may have a unique role in these tasks over and above other areas in the prefrontal cortex. For example, VMF seems particularly important for meta-cognitive judgments and problem-solving in the social domain. Further studies are needed to more sensitively target the VMF's unique contributions to these types of executive functioning.

Cognitive control

Neuropsychological tests

There are many neuropsychological tests that measure aspects of executive function, including: fluid intelligence and IQ (WAIS), verbal fluency (e.g., Controlled Oral Word Association test, phonological verbal fluency), task or set switching (e.g., letter vs. number-naming, Trail Making Test, Wisconsin Card Sorting Task), and response inhibition (e.g., Go/No-go, Stroop). Performance on these tasks is not impacted by damage to the VMF (Abel et al., 2016; Aron, Monsell, Sahakian, & Robbins, 2004; Aron, Sahakian, & Robbins, 2003; Chapados & Petrides, 2013; Gläscher et al., 2012; Keifer & Tranel, 2013; Løvstad et al., 2012; Robinson et al., 2014; Szatkowska, Grabowska, & Szymańska, 2000; Szatkowska, Szymanska, Bojarski, & Grabowska, 2007; Tranel, Manzel, & Anderson, 2008; Tsuchida & Fellows, 2013).

While deficits in a few other tasks have been associated with VMF damage—self- and informant-reported executive functioning in everyday life (Løvstad et al., 2012), semantic fluency (Szatkowska et al., 2000), spatial search (Tsuchida & Fellows, 2013), slower responses in a reaction time task (Arbula et al., 2017), and errors in verbal suppression (Cipolotti et al., 2016; Volle et al., 2011)—deficits in these tasks are also found after damage to other prefrontal regions as well (Løvstad et al., 2012; Szatkowska et al., 2000; Tsuchida & Fellows, 2013). These tasks therefore seem to require multiple prefrontal areas, rather than specifically assessing VMF functioning alone.

ERP studies of response inhibition

There have been three ERP studies of response inhibition in individuals with VMF damage, using the go/no-go, stop-signal and flanker tasks. In the go/no-go task, neither behavioural nor ERP differences were found in the VMF group relative to healthy controls or a lateral prefrontal damaged group (Funderud et al., 2013). In the stop signal task, individuals with VMF damage did not differ behaviourally, but did have a smaller error-related negativity (ERN) and a larger later positive wave (Pe) response to failed inhibitions compared to healthy controls (Solbakk et al., 2014). In the flanker task (Maier, Di Gregorio, Muricchio, & Di Pellegrino, 2015), the VMF group also showed a smaller difference in the negativity between correct and error trials (i.e., delta ERN). While the VMF group showed similar subjective awareness and correction of errors in the flanker task as brain-damaged and healthy controls, they did not show improved accuracy on trials following errors like the other two groups. Thus, while VMF damage does not affect overall performance on response inhibition tasks, it may reduce error-related ERP

components and sequential adjustments of performance after errors. These effects might be linked specifically to damage in rostral and subgenual ACC (Solbakk et al., 2014), and could be relevant to the impairments in feedback learning discussed in the Valuation section.

Reasoning

Several studies suggest that VMF damage impacts different aspects of reasoning. In one study, participants viewed a dot stimulus moving around an array and were asked to generate valid rules for its pattern of movement (Reverberi, D'Agostini, Skrap, & Shallice, 2005). Individuals with medial prefrontal or left lateral prefrontal damage generated fewer abstract rules compared to healthy controls. In another study, both medial and left lateral prefrontal damage led to impairment in making logical inferences from a set of premises (Reverberi, Shallice, D'Agostini, Skrap, & Bonatti, 2009). Notably, however, when only the individuals with intact working memory are considered, those with medial (but not lateral) damage were still impaired and only the medial frontal group was impaired at accurately reporting the difficulty of the task.

Planning and real-Life problem-solving

Two studies have shown evidence of strategic planning and problem-solving deficits in real-life tasks after VMF damage. Individuals with VMF damage made more strategic errors in the Multiple Errands Test (which asks participants to plan errands in a shopping mall) than healthy and non-prefrontal damaged controls, but their performance did not differ from others with prefrontal damage outside VMF (Tranel, Hathaway-Nepple, & Anderson, 2007). In a problem-solving task consisting of real-life scenarios, individuals with VMF damage generated fewer valid solutions to both social and non-social problems, and less effective solutions for social problems in particular, while individuals with other forms of frontal damage produced less effective solutions to the non-social problems (Peters, Fellows, & Sheldon, 2017). In sum, the prefrontal cortex in general is involved in real-life planning and problem-solving, perhaps with a special role for the VMF in problems of a social nature. The VMF's involvement in social decision-making is discussed more extensively in the Social Cognition section below.

Anatomical specificity

Many of the executive function tasks that are not sensitive to VMF damage—for example, effects related to response inhibition, task switch cost, distractibility, and Stroop have been localized to specific regions of the lateral frontal cortices (Aron et al., 2003, 2004; Arbula et al., 2017; Cipolotti et al., 2016; Tsuchida & Fellows, 2013). Many other neuropsychological assessments of executive function are sensitive to damage throughout the prefrontal cortex (Chapados & Petrides, 2013). This suggests that executive functions typically require processes implemented in multiple prefrontal regions.

Emotion

Executive summary

The case of Phineas Gage has given us the lasting image of VMF damage turning a mild-mannered, responsible foreman into an ill-tempered vagabond. Starting with Gage, some of the most striking phenomena associated with VMF damage are changes in affect and personality. The VMF has extensive connections to the amygdala, and has been posited to play an inhibitory role on affective responses generated in the amygdala (Phelps, Delgado, Nearing, & LeDoux, 2004). In self-reports and reports of clinicians and relatives, VMF lesions are associated with social/emotional disturbances (inappropriateness, irritability, anger, aggression, and lack of insight) and diminished motivation (apathy, anhedonia, lack of initiative, lack of persistence)—over and above lesions to other frontal areas. In tasks that involve emotional stimuli, the effects of VMF damage on subjective reports are inconsistent; though there is stronger evidence for altered physiological and neural responses, these have not been fully characterized. The recognition or discrimination of basic emotions from prototypical stimuli is not impaired after VMF damage, though the recognition of emotions from subtle cues is impaired. The cause of this deficit in the recognition of subtle emotions is debated, but it does not appear to be due to disrupted gaze patterns.

Emotional experience

Reported changes in affect and personality

In investigations of personality and affect changes, it is often difficult to tease apart the specific contributions of the VMF, against the typical "frontal" syndrome seen after damage across the prefrontal cortex. Barrash et al. (2011) characterized the emotional/personality effects of VMF damage in terms of three main principal components: disturbed social/emotional behaviour (e.g., social inappropriateness, irritability, aggression, inappropriate affect, and lack of insight), dysexecutive decision-making (e.g., lack of initiative, lack of planning, impulsivity, poor judgment, and perseveration), and diminished motivation/hypo-emotionality (e.g., blunted affect, apathy and withdrawal). Disturbance in these three components has been examined using self-, informant- or clinical-report measures.

For the first factor of disturbed social/emotional behaviour, studies using reports from friends and family find that social inappropriateness, irritability, and lack of insight are all apparent after VMF damage over and above other types of frontal or non-frontal damage (Anderson, Barrash, Bechara, & Tranel, 2006; Barrash et al., 2011; Barrash, Tranel, & Anderson, 2000). In combat veterans, VMF damage was associated with caregiver-reported aggression, possibly dependent on interactions with genetic phenotypes associated with the trait (Pardini et al., 2011, 2014). VMF damage has also been associated with self-reports of increased anger and decreased happiness (Berlin, Rolls, & Iversen, 2005; Berlin, Rolls, & Kischka, 2004; Gillihan et al., 2011), as well as increased informant-rated antisocial behaviour (Bramham, Morris, Hornak, Bullock, & Polkey, 2009). In VLSM analyses, orbitofrontal involvement was found for scales related to disinhibition and self-monitoring for socially inappropriate behaviour (Robinson et al., 2014), cynicism (distrust of others) (Calamia, Markon, Sutterer, & Tranel, 2018), and alexithymia (Campanella, Shallice, Ius, Fabbro, & Skrap, 2014).

For the second factor of dysexecutive decision-making, both lack of initiative and lack of persistence, as assessed by family members, are associated with VMF damage over and above other types of frontal or non-frontal damage (Anderson et al., 2006; Barrash et al., 2000, 2011). In evaluating outcomes of patients who underwent meningioma resections, clinicians note that VMF resections are associated with worse post-operative outcomes in realms like employment and independence, compared with resections elsewhere in the brain (Abel et al., 2016). However, though Harlow evoked an image of an "impatient" and "capricious" Gage after his injury, most studies do not find an increase in reported impulsivity after VMF damage compared to other groups (Anderson et al., 2006; Barrash et al., 2000; Fellows & Farah, 2005b). Individuals with VMF damage who do report increased impulsivity also have extensive damage to other areas in the prefrontal cortex (Berlin et al., 2004; Hornak et al., 2003). There is also mixed evidence on whether VMF damage impacts behavioural tests of impulsivity (e.g., temporal discounting, risk taking), as discussed in the Decision section below.

Finally, for the third factor of hypo-emotionality, apathy and blunted affect, as assessed by family members, are specifically elevated after VMF damage (Anderson et al., 2006; Barrash et al., 2011). Studies of combat veterans with penetrative TBI also found that VMF damage was associated with increased apathy, anhedonia, and fatigue in self- and other-reported scales and clinical assessments (Hogeveen, Hauner, Chau, Krueger, & Grafman, 2017; Pardini, Krueger, Raymont, & Grafman, 2010). In a VLSM analysis, damage to orbitofrontal cortex was specifically correlated with higher apathy scores (Robinson et al., 2014).

In contrast to the emotional deficits observed in other studies, Koenigs et al. (2008) found that combat veterans with VMF injuries had lower instances of post-traumatic stress disorder (PTSD) compared to veterans without brain injuries or with injuries to other parts of the brain (except for veterans with amygdala lesions, who had no instances of PTSD). VMF injury was associated with an overall reduction in intensity and frequency of PTSD symptoms but did not affect other types of anxiety disorder. Likewise, individuals with VMF lesions had fewer symptoms of depression, but specifically with regard to cognitive/affective symptoms like sadness and loss of interest, and not to somatic symptoms like tiredness and loss of appetite (Koenigs et al., 2008). Taking all the findings together, it is possible that while VMF damage generally tends to increase negative emotionality, it also specifically decreases emotions associated with cognitive reflection.

Task related emotional changes

Many studies have investigated the effects of emotion inductions in individuals with VMF damage with various stimuli, such as music, film clips, pictures, and memories; however, the findings have been mixed. Three studies have found that subjective emotional ratings in response to an induction were unaffected in individuals with VMF damage (Gillihan et al., 2011; Hilz et al., 2006; Johnsen, Tranel, Lutgendorf, & Adolphs, 2009). One study found that individuals with large VMF lesions (including both OFC and ACC) reported greater negative affect following negative film clips relative to other prefrontal lesion and healthy control groups (Jenkins et al., 2018). Another study using a social stress test found that individuals with medial prefrontal lesions reported more negative emotions relative to healthy controls, but disrupted physiological responses to stress depended on gender: only the women had elevated cortisol levels after the stress test, whereas men showed increased heart rate and altered heart rate variability after an orthostatic (standing) challenge (Buchanan et al., 2010). In terms of physiological responses to other emotional stimuli after VMF damage, studies have found reduced skin conductance responses (SCR) and changes in heart rate and blood pressure responses to emotionally valenced pictures, music and film clips (Hilz et al., 2006; Jenkins et al., 2018; Johnsen et al., 2009). Thus, there is stronger evidence for disrupted physiological reactivity to emotional stimuli after VMF damage, compared to self-reported emotion. Explicit emotion regulation strategies do not appear to depend on the VMF, however, as deficits in re-appraisal of negative pictures are linked to damage in the dlPFC and dorsal ACC instead (Falquez et al., 2014).

One study suggests that incidental emotion content is processed differently in individuals with VMF damage. The same VMF-damaged individuals who were characterized as having a constellation of emotional changes in Anderson et al. (2006) also participated in a study that involved reading sentences with emotional or neutral content (Burin et al., 2014). When a target sentence was inconsistent with the context of the rest of the short story, healthy controls slowed down for both emotional and neutral sentences. However, individuals with VMF damage only slowed down for inconsistent neutral sentences, not for inconsistent emotional sentences. Similarly, in studies in combat veterans with penetrative brain damage, damage to the polar and orbitofrontal areas was associated with poorer performance in a logical reasoning task, but only with emotional context not neutral content (Eimontaite et al., 2018; Goel et al., 2017). These results show that reasoning relies on several prefrontal regions; discrepancies across studies in the exact role of VMF may be due to differences in lesion location across studies (polar/orbitofrontal versus medial wall).

In addition to disrupted physiological responses, VMF damage has also been associated with changes in the neural response to emotional stimuli, including abnormal insular activation to predictive cues for aversive pictures (Motzkin, Philippi, Wolf, Baskaya, & Koenigs, 2014), potentiated amygdala responses to aversive images (Motzkin, Philippi, Wolf, Baskaya, & Koenigs, 2015), and increased resting perfusion in the bed nucleus of the stria terminalis (Motzkin et al., 2015). These results indicate that VMF damage alters neural networks associated with emotional experience. However, further investigation is needed to explain how these diverse neural findings are linked to changes in personality and affect.

Emotion recognition

Neural bases of emotion recognition

As VMF damage changes one's experience of emotions, it may also impair recognition of emotions in others. In VLSM studies of the neural basis of emotional intelligence, impairments in perceiving prototypical facial emotions were associated with temporal and lateral frontal damage, whereas impairments in managing emotions (understanding the causes of emotions and strategically using them to achieve a goal) were related to damage to posterior OFC, insula, and parietal cortex (Dal Monte et al., 2013; Operskalski, Paul, Colom, Barbey, & Grafman, 2015). Consistent with these VLSM findings, VMF damage does not impair the recognition of basic prototypical emotions in faces (Campanella et al., 2014; Wolf, Philippi, Motzkin, Baskaya, & Koenigs, 2014). Thus, the VMF is not critical for the recognition of prototypical emotions, but parts of the VMF are critical for more social cognitive aspects of emotion understanding, including how emotions can be used in a goal-oriented way.

Recognition of subtle emotions

In contrast to findings in recognition tasks that use prototypical examples of emotions, VMF does appear critical for recognizing emotion from subtle cues. Studies using either low intensities of emotions (i.e., morphs between neutral and emotional expressions) or short exposures (500ms) have found that individuals with VMF damage are impaired at emotion recognition (Heberlein, Padon, Gillihan, Farah, & Fellows, 2008; Jenkins et al., 2014; Tsuchida & Fellows, 2012; Willis, Palermo, McGrillen, & Miller, 2014), though some studies only find effects for certain emotions such as anger or disgust (Vaidya & Fellows, 2019; Wolf, Pujara, Baskaya, & Koenigs, 2016). Perhaps consistent with problems recognizing emotions from subtle cues, medial frontal lobe damage broadly (either dorsomedial or orbitofrontal) also impairs the recognition of vocal emotion (Hornak et al., 2003).

Deficits in the recognition of emotion from subtle facial cues appear to be specific to VMF damage. In a VLSM analysis, the strongest effects were in medial OFC, specifically the gyrus rectus (Tsuchida & Fellows, 2012). Jenkins et al. (2014) also examined anatomical specificity within the VMF, dividing individuals according to whether their lesions were in ACC (in this case, dorsomedial frontal lesions), OFC, or VMPFC (i.e., including both ACC and OFC). They found significant emotion recognition impairments only in the VMPFC group, with a similar trend in the OFC group.

What could be the mechanism behind this deficit in the recognition of subtle emotions from faces? Wolf et al. (2016) proposed that individuals with VMF damage do not look at the eyes as much as healthy controls, similar to the explanation for why individuals with amygdala lesions do not recognize facial expressions of fear (Adolphs et al., 2005). Participants with VMF damage in the Wolf et al. (2016) study did improve their recognition of angry emotions when they were instructed to focus their gaze on the eye region. However, another study using eye-tracking found that individuals with VMF damage did not differ in any fixation patterns at facial features than control groups and that directing eye gaze did not alter emotion recognition performance (Vaidya & Fellows, 2019). Thus, it is still an open question why VMF damage causes difficulty in recognizing subtle emotional cues. Instead of causing individuals to seek information differently from facial expressions, VMF lesions may instead affect the interpretation of emotional cues.

Distinguishing between emotions and recognition of complex emotions

In contrast to the recognition of basic emotions from subtle facial or vocal cues, VMF does not appear to be critical for emotion discrimination or the recognition of complex emotions. VMF damage did not impair the ability to distinguish emotions when presented with faces of varying morphs between different distinct emotions (e.g., happiness and surprise) (Hornak et al., 2003). Rather than VMF damage, deficits in emotion discrimination have instead been attributed to damage to the ventrolateral prefrontal cortex and to disruption of fibres of passage connecting orbitofrontal to temporal and occipital cortices (Philippi, Mehta, Grabowski, Adolphs, & Rudrauf, 2009; Tsuchida & Fellows, 2012). Shaw et al. (2005) examined the recognition of complex emotions (e.g., pensive, flirtatiousness, suspicious) from pictures of eye regions in the same participants studied in Hornak et al. (2003). They found that damage to the right lateral prefrontal cortex impaired the identification of negative social emotions relative to healthy controls. However, a larger VLSM study subsequently found effects only in the temporo-parietal junction, a region often linked to theory of mind (Campanella et al., 2014).

Relationship between emotional experience and emotion recognition

Reduced sensitivity to the emotions of others could be a consequence of reduced insight into one's own emotions. VMF damage has been linked to alexithymia, the deficit in recognizing emotion in oneself and others (Campanella et al., 2014). Several studies have suggested that individuals whose emotional experiences have been impacted by their lesions also have trouble recognizing the same experiences in others: individuals with bilateral OFC lesions or lesions in the ACC had marked changes in both emotional experience and emotion recognition in Hornak et al. (2003); prefrontal-damaged individuals who experienced less intense emotions on a sadness induction task were also impaired at recognizing sad expressions (Heberlein et al., 2008); individuals with VMF damage who reported stronger emotional changes after watching emotional film clips (Jenkins et al., 2018) were also worse at emotion recognition (Jenkins et al., 2014). The mechanism linking one's own emotional experiences to those of others may

involve theory of mind and empathy, which we will discuss in the next section.

Anatomical specificity

As the medial network of the VMF is more interconnected with the amygdala than the orbital network, one might expect that damage to the medial network has a greater impact on affective responses. It has also been suggested that the OFC mediates more simple emotional responses, whereas the ACC mediates more complex, social emotional functions (Rudebeck, Bannerman, & Rushworth, 2008). However, the evidence here does not clearly support either of these hypotheses. VLSM analyses place effects on apathy, disinhibition, and emotion recognition in the orbitofrontal cortex. However, studies with separate groups with lesions in distinct regions of the VMF conclude that both lesions restricted to the OFC and lesions including the ACC cause more negative affect, but could have different effects on physiological and subjective emotional reactions to induced emotion and on emotion recognition (Hornak et al., 2003; Jenkins et al., 2018).

Social cognition

Executive summary

Neuroimaging studies of social cognition have implicated the medial frontal lobe, along with the temporo-parietal junction (TPJ), medial parietal cortex, and lateral temporal lobes (Schaafsma, Pfaff, Spunt, & Adolphs, 2015; Spreng, Mar, & Kim, 2009). As reviewed in the Emotion section, individuals with VMF damage experience personality alterations involving social inappropriateness and exhibit deficits in recognizing emotions from subtle cues. In tasks that directly assess social cognition and behaviour, individuals with VMF damage are more socially inappropriate and misjudge social norms. VMF damage also leads to deficits on tasks that require theory of mind or mentalizing, though these deficits are more apparent when the content is social (e.g., recognizing faux pas or sarcasm) than in direct assessments of others' thoughts and beliefs. Individuals with VMF damage make moral judgments that are more utilitarian and that focus more on outcomes than on intentions. The evidence on the impacts of VMF damage on social preferences and social attitudes is mixed and less consistent.

Social perception

VMF damage does not affect social trait judgments. Individuals with VMF damage are unimpaired in judgments of dominance from photos of faces or video interactions, though they did use a smaller range on the scale (Karafin, Tranel, & Adolphs, 2004). Individuals with damage to the lateral OFC were unimpaired in judging perceived attractiveness and competence in pictures of politicians (Xia, Stolle, Gidengil, & Fellows, 2015). However, these individuals' subsequent preferences in a voting task were less likely to reflect competence judgments, compared to others with frontal damage and healthy controls, suggesting the VMF may be involved in using social perceptions to make social decisions.

There is stronger evidence linking VMF damage to misjudging appropriate social interactions. In a virtual reality task (Pullen, Morris, Kerr, Bullock, & Selway, 2006), individuals with OFC damage were not impaired at avoiding an obviously socially awkward situation (cutting in between two people talking to each other), but were marginally more likely than people with other kinds of frontal damage to take a socially awkward route in a less obvious situation (cutting in between two people who were not interacting but standing close together). When individuals with VMF damage were asked questions about cartoon depictions of social interactions, they performed more poorly than healthy controls in matching facial and physical expressions or completing a social interaction based on previous panels (Mah, Arnold, & Grafman, 2005). In another test with videotaped interactions, damage to multiple prefrontal regions, including OFC, was linked to poor performance (Mah, Arnold, & Grafman, 2004). VMF damage is also associated with impaired explicit knowledge of social norms (Robinson et al., 2014).

Emotional and cognitive empathy

Emotional empathy

Damage to the VMF does not impact self-reported emotional empathy, or the ability to resonate with other people's emotions. In a VLSM analysis, Robinson

et al. (2014) found that self-reported empathic concern was not associated with VMF damage, but rather with broadly lateralized right hemisphere damage. Another VLSM study of self-reported emotional empathy also did not find VMF involvement, instead implicating the temporal lobes and insula (Driscoll, Dal Monte, Solomon, Krueger, & Grafman, 2012). A significant caveat to the conclusion that VMF is not necessary for emotional empathy, however, is that no studies have yet examined emotional empathy with task-based or physiological measures.

Theory of mind

Theory of mind, or mentalizing, is the ability to understand other people's thoughts, beliefs and feelings. There is some evidence that VMF damage impacts mentalizing, though the effects are task-dependent. The Robinson et al. (2014) VLSM study found that self-reported perspective-taking abilities were associated with damage to VMF or the bilateral anterior temporal cortex. However, most studies have examined theory of mind using vignette tasks.

One task that has been widely used to study theory of mind is the faux pas task (Stone, Baron-Cohen, & Knight, 1998), which asks people to detect whether someone has said something awkward or hurtful. The faux-pas task contains both cognitive and affective components, requiring the subject to understand both the mental state of the person who made the faux-pas (*i.e.*, he did not know that he should not have said what he did), and the person who hears it (*i.e.*, she should be hurt or insulted). Studies using this task have found that individuals with VMF damage performed worse than healthy controls in detecting the faux pas (Lee et al., 2010; Leopold et al., 2012). Lee et al. (2010) found that individuals with medial prefrontal damage specifically performed worse than individuals with lateral prefrontal or non-frontal damage on questions about the mental state of the person committing the faux-pas.

Interestingly, the faux pas task is quite similar to some of the tasks discussed above that assess appropriate social interactions. Other tasks that try to more directly isolate mentalizing have found less convincing for VMF involvement. Detecting sarcasm, for example, requires understanding what the speaker believes about the listener's beliefs. Channon et al. (2007) investigated the ability to detect direct sarcasm (where the intended meaning is a direct reversal from the literal meaning, e.g., in a story where friends went to a terrible play, "That was a fantastic play you took me to see!") and indirect sarcasm (where the intended meaning is indirectly related to the reversal of the literal meaning, e.g., in a story where an overly competitive friend lost a tennis match, "I suppose you'll say there is a hole in your racket!"). The authors found that individuals with frontal lobe damage performed worse overall relative to healthy controls, with medial and lateral orbital damage related to deficits in detecting direct sarcasm in multiple choice questions and inferior frontal damage related to deficits in sarcasm detection in free response questions.

In vignette tasks that require perspective-taking (e.g., in a story where a burglar who just robbed a store is approached by a policeman who only had seen that he dropped a glove, "why did the burglar give himself up?"), one study found that individuals with VMF damage were impaired in mentalizing about thoughts but not feelings (Jenkins et al., 2014), while another study did not find any effects of VMF damage (Leopold et al., 2012). VLSM and symptom-lesion correlation studies that used similar tasks found that deficits were related to ventrolateral damage, as well as damage to the frontostriatal tract and superior longitudinal fasciculus (Channon et al., 2007; Nakajima et al., 2018). Thus, in tasks that use vignettes to directly query knowledge of others' thoughts and feelings, there is less evidence for VMF involvement.

Communication

Deficits in theory of mind or the perception of social appropriateness could impact communication, and there is some evidence that impairments after VMF damage manifest in communication with others. In one study, individuals with VMF damage dominated a natural conversation (i.e., spoke the most words per turn), whereas healthy controls or individuals with MTL damage would converge with their interlocutor and make more equal conversational exchanges (Gordon, Tranel, & Duff, 2014). This study points to a potential unique role for the VMF (in contrast to the MTL) in monitoring and regulating social behaviour. However, this study's participants were same ones identified previously characterized as having increased levels of social inappropriateness (Barrash

et al., 2000), so it is not clear if other individuals with VMF damage without a social syndrome would display the same behaviour.

In contrast to turn-taking in natural conversation, the ability to communicate successfully with a partner in order to coordinate in solving a problem is not affected by VMF damage (Gupta, Tranel, & Duff, 2012; Stolk, D'Imperio, Di Pellegrino, & Toni, 2015). Gupta et al. (2012) assessed successful communication and the degree of verbal play (e.g., telling jokes or puns, singing songs) in a collaborative problem-solving task that required verbal communication with a partner. Individuals with VMF damage were not impaired in communicating effectively to solve this task, nor did they differ in verbal play. In a similar task, Stolk et al. (2015) asked participants to solve a problem with an unseen collaborator, who was either said to be a small child or an adult. Individuals with VMF damage successfully communicated to solve the problem, though they did not adjust their communicative style to the perceived age of the addressee.

Moral judgment

Individuals with VMF damage show altered moral judgments. Many of these studies use variants of the classic "trolley problem." For certain high emotion and high conflict scenarios—for example, whether you would sacrifice one person by pushing them in front of a runaway trolley in order to save the lives of five others—healthy controls rarely endorse the utilitarian answer (sacrificing one person to save five, 10%–20% endorsement). In contrast, individuals with VMF damage endorse the utilitarian answer much more often (around 50%–60% endorsement) (Ciaramelli, Muccioli, Làdavas, & di Pellegrino, 2007; Koenigs et al., 2007; Moretto, Làdavas, Mattioli, & di Pellegrino, 2010; Taber-Thomas et al., 2014; Thomas, Croft, & Tranel, 2011). VMF damaged participants are quicker to reach these decisions than healthy controls (Ciaramelli et al., 2007) and lack an increased SCR preceding the decision (Moretto et al., 2010). Thus, VMF-damaged participants appear to lack the emotional response that controls have to these dilemmas. These behavioural differences were specific to moral dilemmas in which there was conflict between deontological and utilitarian principles (e.g., "smothering a baby to save the lives of many others"), and did not extend to dilemmas without this conflict (e.g., "abandon one's baby to avoid the burden of caring for it") (Koenigs et al., 2007). Individuals with VMF damage were more utilitarian than healthy controls for all high-conflict scenarios, whether harm was directly inflicted (pushing the person off a footbridge in the trolley problem) or only indirect (pulling a switch to direct the trolley towards the person) (Thomas et al., 2011).

Taber-Thomas et al. (2014) compared individuals who had VMF damage during childhood versus adulthood. While individuals whose lesions occurred in adulthood were not more likely to endorse self-serving actions (e.g., cheating on one's taxes to save money), individuals whose lesions occurred in childhood were more likely to endorse them. This tendency increased with earlier age of onset, suggesting that VMF may serve a role in moral development.

One reason individuals with VMF damage might be more utilitarian is that they focus on outcomes more than intentions (Channon et al., 2010; Ciaramelli, Braghittoni, & di Pellegrino, 2012; Young et al., 2010). Compared to individuals with non-frontal damage or healthy controls, individuals with VMF damage judged failed attempts to harm (intention to harm without actual harm) to be more morally permissible and judged accidental harm (no intention to harm with actual harm) to be less morally permissible. These results suggest that individuals with VMF damage do not consider the mental states of the individual making the decision and only focus on whether the outcome was good or bad. Congruent with this idea and suggesting a broader de-emphasis of social context, individuals with VMF damage were more accepting of socially-marginalized individuals who committed no bad actions, but showed comparable disgust at morally deviant actions conducted by individuals of prominent social standing (Ciaramelli, Sperotto, Mattioli, & di Pellegrino, 2013).

In a task where participants made moral judgments about a target both before and after they were told about an incident involving that target (committing a good or bad action), individuals with VMF damage updated their assessment in response to the new information to a lesser degree than brain-damaged controls, while a hippocampal-damaged group showed exaggerated updates (Croft et al., 2010). This result is congruent with the VMF's role in value updating discussed below (De Araujo, Rolls, Velazco, Margot,

& Cayeux, 2005; Plassmann, O'Doherty, Shiv, & Rangel, 2008), and further studies of how social or moral judgments are made and updated would be useful.

Importantly, few of the above studies of moral judgment included a control group of individuals with damage to other parts of frontal cortex, and a complex behaviour like moral judgment is likely to involve multiple prefrontal areas. Indeed, a VLSM study in combat veterans showed that multiple prefrontal regions—DLPFC, DMPFC, VLPFC, as well as VMPFC—are linked to judgments regarding third-party punishment (punishing someone for committing a crime against another person) (Glass, Moody, Grafman, & Krueger, 2015). Future studies on moral judgment should include controls with frontal damage outside of the VMF to test the unique contribution of the VMF in this domain.

Social attitudes

Beyond moral judgment, how does VMF damage alter social and political attitudes? Though a few studies have found that VMF damage increases implicit and explicit bias, the effects across studies are mixed and are not specific to VMF within the frontal lobe. On implicit measures, damage to the VMF has been linked to sexist attitudes (Forbes et al., 2011; Gozzi, Raymont, Solomon, Koenigs, & Grafman, 2009; Milne & Grafman, 2001). However, different regions of the VMF (i.e., medial vs. lateral OFC) seem to have opposing effects on this measure (Gozzi et al., 2009), and another implicit bias, towards increased violence, has been linked to other regions such as DLPFC and inferior posterior temporal lobe (Cristofori et al., 2016). For explicitly expressed bias, individuals with VMF damage made more positive judgments of radical political statements and scored higher on traits of authoritarianism and fundamentalism (Asp, Ramchandran, & Tranel, 2012; Cristofori et al., 2015). However, these effects have also been found after DLPFC damage (Zhong, Cristofori, Bulbulia, Krueger, & Grafman, 2017). Thus, VMF damage does not uniquely cause increased bias on either implicit or explicit measures.

Decision-making under social conditions

Social economic tasks

Social economic tasks bridge social cognition and value-based decision-making. Studies typically use common experimental economic games such as the dictator, ultimatum, public goods and trust games. In the dictator game, one participant decides how to divide a monetary stake between themselves and an anonymous partner. In the ultimatum game, a proposer offers a division of the stake, which the responder may accept or reject, but rejection results in neither player receiving any money. In the public goods game, multiple participants decide how much to contribute to a group pot, which is multiplied and split equally amongst all participants, and how much to keep for themselves. Finally, in the trust game, an investor decides how much money to send to a trustee, with the amount transferred being multiplied, and then the investee must decide how much of the increased amount to send back to the investor.

Though early findings in these paradigms suggested that VMF damage leads to more anti-social behaviour (Koenigs & Tranel, 2007; Krajbich, Adolphs, Tranel, Denburg, & Camerer, 2009; Moretti, Dragone, & di Pellegrino, 2009), more recent work has complicated this picture (Gu et al., 2015; Moretto, Sellitto, & di Pellegrino, 2013; Wills et al., 2018). Koenigs and Tranel (2007) found that individuals with VMF damage and "acquired sociopathy" were more likely to reject unfair offers in the ultimatum game. The same individuals gave less in the dictator game, and demanded as responders the same amount that they offered as proposes in the ultimatum game (whereas healthy subjects typically offer more than they demand) (Krajbich et al., 2009). These findings were interpreted as an insensitivity to guilt. Moretti et al. (2009) replicated the finding that individuals with VMF damage reject unfair offers in the ultimatum game at a higher rate. However, when the offers were delivered in a concrete manner, as an envelope of cash handed to the participant, individuals with VMF damage were no more likely to reject than healthy controls. In direct contrast to Koenigs and Tranel (2007) and Moretti et al. (2009), though, Gu et al. (2015) found that individuals with VMF damage were less likely to reject unfair offers in the ultimatum game. More recent studies have also found conflicting results regarding prosocial behaviour after VMF damage, with VMF damage being associated with lower back transfers when acting as trustees in the trust game (Moretto et al., 2013), but with greater contributions in a public goods game (whereas DLPFC damage was associated with lower contributions) (Wills et al., 2018).

One interesting and consistent finding in these studies is that individuals with VMF damage behave similarly when interacting with human or computer partners. In the trust game, healthy controls and frontal controls invested more money with computer than human partners, displaying an aversion to betrayal, whereas individuals with VMF damage invested similar amounts in both conditions [and thus more money in the human condition than the two control groups, (Moretto et al., 2013)]. In Moretti et al. (2009), healthy control participants were less likely to reject computer-generated offers in the ultimatum game, while individuals with VMF damage rejected computer-generated offers as often as human ones. These results suggest that individuals with VMF damage are considering the social aspects of these tasks to a lesser degree, and perhaps focusing on outcomes more than mental states as discussed above for moral judgments.

Decision-making under social influence

Chen, Rusch, Dawson, Rizzo, and Anderson (2015) used a driving simulation task to assess the impact of VMF damage on social influence. Participants were asked to make left turns into traffic with varying sized gaps between the cars, either with or without a truck honking behind them. Individuals with VMF damage had elevated SCR and chose smaller (and potentially unsafe) gaps under social pressure compared to individuals with other brain damage and healthy controls. These results suggest a greater susceptibility to social pressure or a greater impulsivity under emotional conditions after VMF damage.

Anatomical specificity

The specificity of many of the above effects on social cognition to VMF damage has yet to be established, as many studies have included a control group with damage elsewhere in the frontal lobe. The specificity of these effects within VMF is also an important question for future work—most studies examined individuals with damage across medial regions (BA 10, 11, 24, and 32), though a couple of studies localized effects to the lateral OFC (Gozzi et al., 2009; Xia et al., 2015). Another complicating factor in interpreting several lesion studies in this section is that they involve participants initially selected specifically because of documented social and emotional changes (Ciaramelli et al., 2007, 2012; Croft et al., 2010; Gupta et al., 2012; Koenigs et al., 2007; Koenigs & Tranel, 2007; Krajbich et al., 2009; Moretti et al., 2009; Moretto et al., 2010; Thomas et al., 2011; Young et al., 2010). Thus, an open question for future research is the extent to which these findings reflect VMF damage in general versus a subset of VMF damage associated with a pronounced syndrome involving marked social impairment.

Valuation

Executive summary

Building off a seminal series of studies using the Iowa Gambling Task, some of the most well-studied effects of VMF damage involve valuation, including both value-based learning and decision-making. The VMF is necessary for some aspects of the initial learning of probabilistic stimulus-reward associations. Consistent with lesion studies in non-human primates, VMF damage in humans impairs learning about reversals of contingencies and reward devaluation (updating second-order associations). In value-based decision-making, individuals with VMF damage are more inconsistent in their choices, which might be linked to changes in how they gather, weight and integrate information. Findings regarding intertemporal and risky decisions are more mixed, though the balance of the evidence suggests that individuals with VMF damage are more risk-seeking and less regret-prone. Finally, individuals with VMF damage are less sensitive to the effects of reward on attention.

Learning

Iowa Gambling Task

Bechara, Damasio, Damasio, and Anderson (1994) developed the Iowa Gambling Task (IGT) to investigate value-based learning and decision-making after VMF damage. In the IGT, participants choose cards from four different decks. Different cards provide different amounts of gain or loss, and participants try to earn as much money as possible. Some decks are advantageous, providing smaller gains but also smaller losses, leading to a net gain overall. Others are disadvantageous, providing big gains but even bigger losses, leading to a net loss overall. Subjects must

learn the overall value of each deck through experience, integrating probabilistic outcomes over many trials. Bechara et al. (1994) found that individuals with VMF damage choose the disadvantageous decks more often than healthy controls, a robust phenomenon that has been replicated across many years and different versions of the task (Abel et al., 2016; Waters-Wood, Xiao, Denburg, Hernandez, & Bechara, 2012; Xiao et al., 2013) though see (Sanfey, Hastie, Colvin, & Grafman, 2003). Individuals with VMF damage also fail to show the differential SCR to advantageous vs. disadvantageous decks that is observed in healthy controls.

However, in addition to VMF, other areas of prefrontal cortex are also critical to IGT performance. In a VLSM study with 344 individuals (165 with frontal damage), Gläscher et al. (2012) found that lower scores on the IGT were associated with ventromedial frontal damage, as well as damage in some areas of the dorsomedial and lateral prefrontal cortices. Other studies have also found that individuals with frontal damage in different areas (VMPFC, DLPFC, or both) all show deficits on the IGT (Fellows & Farah, 2005a; Ouerchefani, Ouerchefani, Allain, Ben Rejeb, & Le Gall, 2017).

The IGT involves both deterministic and probabilistic outcomes, as well as apparent changes in stimulus-reward contingencies. Thus, to better understand the particular contribution of the VMF to reward-based learning, the studies discussed in the following sections have isolated and examined these different aspects of reward learning.

Initial discrimination learning

Individuals with VMF damage are able to learn simple deterministic associations between stimuli and reward (Fellows & Farah, 2003). When these associations are probabilistic, some studies have found that individuals with VMF damage are impaired (Camille, Tsuchida, & Fellows, 2011; Tsuchida, Doll, & Fellows, 2010), while others have not (Hornak et al., 2004; Kumaran, Warren, & Tranel, 2015). VMF damage is also associated with impaired choices between stimuli with learned probabilistic associations, though only for stimuli associated with negative outcomes (Wheeler & Fellows, 2008). It is not clear what underlies the contradictory findings for learning probabilistic associations, as the studies that found impairments (Camille et al., 2011; Tsuchida et al., 2010) involved more discriminable probabilities (the "good deck" is rewarded 6/7 times and the "bad deck" the reverse) than those did not (the "good deck" was rewarded 70% of the time and the "bad deck" 40%; Hornak et al., 2004; Kumaran et al., 2015), and there were no obvious differences in lesion location between these studies.

Camille et al. (2011) showed regional specificity within the medial prefrontal cortex for learning the value of stimuli versus the value of actions. Individuals with lesions in the orbitofrontal cortex had difficulty learning which of two stimuli (i.e., a blue versus yellow card deck) was probabilistically associated with reward, but had no problems in a similarly structured task that involved learning the value of actions (i.e., supination versus pronation of the wrist). In contrast, individuals with dorsomedial frontal lesions displayed the opposite pattern, with impairment in action but not stimulus learning.

When stimuli are multidimensional, the VMF is critical for learning the relationship between the relevant attributes and reward, but is not necessary to suppress the influence of irrelevant attributes. In Chase et al. (2008), participants first learned a set of reward associations for stimuli that had two attributes, only one of which was predictive of reward, and were then tested in a transfer task where the irrelevant attributes of the stimuli were changed. Individuals with VMF damage made more errors when learning new associations, but had no difficulty with the transfer test. This finding was corroborated by Vaidya and Fellows (2016), who found that individuals with VMF damage were worse at learning about the relevant attributes in a multidimensional learning task, but were not abnormally influenced by the irrelevant attributes. In contrast, individuals with lateral prefrontal damage were unduly influenced by irrelevant attributes.

Reversal learning

In the original version of the IGT, the disadvantageous decks initially yield a run of high rewards, leading an initial preference to develop that must later be overcome when future losses make these same decks no longer favorable. On a "shuffled" version of the IGT, which does not demand such a reversal since the losses are apparent early, individuals with VMF

damage are no longer impaired, while those with dorsolateral damage are still impaired (Fellows & Farah, 2005a). Thus, impairments on the IGT after VMF damage may be traced to a general difficulty in learning the reversal of reward contingencies.

Deficits in reversal learning after VMF damage have been reliably demonstrated for both deterministic (Fellows & Farah, 2003) and probabilistic associations (Berlin et al., 2004, 2005; Hornak et al., 2004; Tsuchida et al., 2010; Camille et al., 2011), with one exception (Kumaran et al., 2015). These deficits could arise from failures to extinguish previously learned associations in favour of new ones, which has been correlated with poor orientation for space and time in neuropsychological assessments (Nahum, Ptak, Leemann, & Schnider, 2009). In a VLSM analysis of 39 prefrontal damaged subjects, Tsuchida et al. (2010) found that reversal learning deficits were associated with damage in posteromedial OFC and, to a lesser extent, right lateral PFC. From studies of lesions in non-human primates, this deficit is thought to be due to the disconnection of fibres of passage in this region (Rudebeck, Saunders, Prescott, Chau, & Murray, 2013).

Contingency learning

Difficulty in probabilistic and reversal learning could indicate an impairment in the ability to integrate reward feedback over time. Several studies have used reinforcement learning models to study the influence of past outcomes on choices and have associated different parts of the VMF with different aspects of this process. Both Kovach et al. (2012) and Noonan, Chau, Rushworth, and Fellows (2017) used multi-armed bandit tasks, and showed that individuals with damage to the frontopolar cortex or lateral OFC, respectively, were less influenced by the reward outcome on the most recent previous choice during learning. Meanwhile, damage to the medial portion of the OFC does not impair the learning of recent reward contingencies, but instead impairs subjective ratings of the differences between levels of reward (Kumaran et al., 2015; Noonan et al., 2017; O'Callaghan, Vaghi, Brummerloh, Cardinal, & Robbins, 2019). Supporting these results, the choices of individuals with damage to ventral medial prefrontal regions were sensitive to recent rewarding outcomes on the IGT, but notably, those with ventral lateral damage were not (Hochman, Yechiam, & Bechara, 2010). In sum, damage to the lateral and anterior OFC, but not medial OFC, specifically impair learning from recent past outcomes, whereas medial OFC may be important for subjective awareness of differences in the value of options.

Devaluation

In the devaluation paradigm, participants first learn the relationship between a conditioned stimulus and a reward (e.g., press a red button for M&M candy), then experience a decrease in the desirability of the reward (e.g., eat M&Ms until they are satiated), and are tested on transferring this decrease in reward value to the associated stimulus (e.g., no longer press the red button). Whereas reversal learning involves adapting to changes in the contingency between stimulus and outcome, devaluation involves adapting to changes in outcome value (while the contingency stays the same). Reber et al. (2017) found that individuals with VMF lesions showed impaired devaluation of conditioned stimuli associated with food. This is consistent with lesion studies in non-human primates, where lesions to central orbitofrontal cortex (areas 13 and 11) disrupt devaluation (Izquierdo, Suda, & Murray, 2004; Rudebeck & Murray, 2011).

Decision-making

Future-oriented decisions

Bechara et al. (1994) suggested that impairments in the IGT may be due to lack of foresight or "myopia for the future". Bechara, Tranel, and Damasio (2000) used a variant of the IGT that had greater immediate punishment (but greater future reward) in the advantageous decks and lower immediate punishment (but lower future reward) in the disadvantageous decks, and found that individuals with VMF damage, just as with the original IGT version, chose from the disadvantageous deck more often—suggesting that they react only to immediate consequences and are insensitive to future outcomes. Others have sought to study potential aspects of myopia for the future without the learning component of the IGT.

Several studies have measured the extent to which delayed rewards are discounted after VMF damage by giving participants choices between smaller immediate and larger delayed rewards. Individuals with VMF damage did not differ from controls in temporal discounting in two studies (Fellows & Farah, 2005b; Leland & Grafman, 2005), but did discount future

rewards more steeply in a third (Sellitto, Ciaramelli, & di Pellegrino, 2010). Two possibilities could underlie the discrepancy between these studies. Sellitto et al. (2010) posited that the participants in their study and Fellows and Farah (2005b) differed in lesion location, with greater OFC involvement in the former (associated with increased discounting) and more medial prefrontal involvement in the latter. Another possibility is that individuals with VMF lesions are simply more variable in their choices, manifesting in different results in different studies (Fellows, 2011).

One of the processes hypothesized to impact temporal discounting is the ability to imagine the future (Peters & Büchel, 2010). As discussed in the Memory section, individuals with VMF damage construct less detailed future scenarios (Bertossi, Aleo, et al., 2016). When prompted to think of future events, individuals with VMF lesions also think of events that are less far into the future, compared to healthy controls or individuals with damage outside the frontal lobe (Fellows & Farah, 2005b). In addition to a foreshortened prospective time horizon, individuals with VMF damage also overestimate the passage of time (Berlin et al., 2004), which could additionally lead to increased discounting of future rewards (Zauberman, Kim, Malkoc, & Bettman, 2009).

Risk and uncertainty

Another potential component of poor IGT performance is risk taking. Many studies have examined the effects of VMF damage on risky decision-making. Several of these use the Cambridge Gambling Task (CGT), which removes the learning component of the IGT and makes the odds explicit. Participants see a number of square that are red or blue and must decide which colour to bet on and how much to bet. The results from this paradigm are somewhat inconsistent. In an early study, Rogers et al. (1999) found that individuals with orbitofrontal damage placed smaller bets and chose the unlikely outcome more often, relative to healthy controls and those with frontal damage elsewhere. Subsequently, Manes et al. (2002) reported that individuals with large prefrontal lesions placed larger bets, while those with lesions restricted to the OFC showed no difference. Clark et al. (2008) and Studer, Manes, Humphreys, Robbins, and Clark (2015) found that individuals with VMF damage placed larger bets, but Studer et al. (2015) reported that they adjusted the size of their bet less in response to different odds, while Clark et al. (2008) did not find this effect.

Larger bets in the CGT would be consistent with an increased tolerance for risk, and two other studies using different paradigms have found increased risk taking after VMF damage (Hsu, Bhatt, Adolphs, Tranel, & Camerer, 2005; Weller et al., 2007), though other studies did not (Leland & Grafman, 2005; Levens et al., 2014). Pujara, Wolf, Baskaya, and Koenigs (2015) found increased risk taking in VMF damaged individuals, but only when choosing between losses, and not when choosing between gains. This pattern reflects an exaggeration of the typical reflection effect (risk seeking in losses, risk aversion for gains) observed in healthy individuals (Kahneman & Tversky, 1979). Spaniol, Di Muro, and Ciaramelli (2019) found increased risk-taking after VMF damage, but only for the "hot" version of their task (where participants turn over cards one a time, busting when a loss card appears) not the "cold" version (where participants commit ahead of time to how many cards they want to turn over).

Thus, there seems to be some tendency for VMF damage to increase risk-taking, though the findings across studies are not entirely consistent and may depend on different aspects of the tasks or participants' lesions. In contrast to other aspects of risk-taking, VMF damage does not alter the gambler's fallacy, in which individuals believe in a dependence between independent outcomes (this tendency is instead reduced after insular damage) (Clark, Studer, Bruss, Tranel, & Bechara, 2014).

Regret

Another series of studies has examined the affect experienced after the outcomes of risky decisions are revealed. Camille et al. (2004) asked participants to choose between two gambles, and then either displayed the outcome of the chosen gamble only, or both gambles. In healthy controls, an unfavourable result from the chosen gamble induced disappointment, whereas an unfavourable comparison between the outcomes of the chosen and unchosen gambles induced regret. In contrast, subjects with VMF damage were insensitive to regret. This result was replicated in a later study with a larger sample (Larquet, Coricelli, Opolczynski, & Thibaut, 2010). Levens et al. (2014) found that regret insensitivity was specific to damage to the lateral OFC.

Choice consistency

Beginning with Phineas Gage, who was described after his injury as "capricious and vacillating" (Harlow, 1868), inconsistency has long been thought of as a hallmark of VMF damage. Making consistent choices is also the central feature of economic rationality and utility maximization (Samuelson, 1937). Several studies have now shown that individuals with VMF damage are more likely to make inconsistent or intransitive choices, such as choosing A over B, B over C, and then C over A (Camille, Griffiths, Vo, Fellows, & Kable, 2011; Fellows & Farah, 2007; Henri-Bhargava, Simioni, & Fellows, 2012). These effects are reliable, but not large, suggesting that individuals with VMF damage are more likely to make errors or assess value in a noisy manner, rather than to choose using a fundamentally intransitive mechanism.

Other studies have examined the consistency of liking or preference ratings. When evaluating paintings, individuals with VMF damage are not less likely to make choices inconsistent with their ratings (Vaidya & Fellows, 2015a). However, when making repeated ratings, individuals with VMF damage show more inconsistency when evaluating potential hypothetical spouses but not when evaluating potential hypothetical houses (Bowren, Croft, Reber, & Tranel, 2018). These results suggest that inconsistency after VMF damage might vary across categories, in a manner that could shed light on the nature of the deficit, though this idea needs to be explored more in future research.

Decision confidence

Functional imaging and neural recording studies have implicated the VMF in decision confidence (De Martino, Fleming, Garrett, & Dolan, 2013; Kepecs, Uchida, Zariwala, & Mainen, 2008). Two studies have examined the effects of VMF damage on self-reported confidence, and found mixed effects (Gomez-Beldarrain, Harries, Garcia-Monco, Ballus, & Grafman, 2004; Scherer, Taber-Thomas, & Tranel, 2015). In Scherer et al. (2015), participants chose a photograph that they thought other people would prefer, and then chose to read positive or negative reviews about that picture. Individuals with VMF damage made similar preference and confidence judgments and exhibited a similar bias for favorable reviews, but took longer than healthy or brain damaged control to select the reviews to read. Individuals with OFC damage in a different study were overconfident compared to healthy controls in making predictive decisions, though the same was the case with the other groups with brain damage (dorsolateral and parietal) in the study (Gomez-Beldarrain et al., 2004).

Decision processes

VMF damage has several effects on how people gather, weight, and integrate information in order to reach a decision. Fellows (2006) examined how people gather information in a multi-attribute, multi-alternative choice problem. Healthy participants tended to search for information by attribute, assessing a single attribute at a time across all options. In contrast, individuals with VMF damage tended to search for information by option, assessing a single option at a time on all attributes.

Other studies have shown that VMF damage can alter how different attributes are weighted in a decision. In rating paintings, VMF-damaged participants gave less weight to certain attributes (involving the emotion and complexity of the work) compared to healthy and frontal controls (Vaidya, Sefranek, & Fellows, 2017). This differential weighting was linked to pre-genual ACC damage in a VLSM analysis. In choosing between politicians (based on photos alone), individuals with VMF damage appeared to give less weight to perceived competence (Xia et al., 2015). To the extent that VMF damage alters intertemporal or risky decision-making, as discussed above, this could also be explained in terms of a differential weighting of attributes (amounts versus delays or probabilities).

VMF may be particularly necessary, though, when value cannot be assessed by a simple weighted combination of attributes. In a recent study (Pelletier & Fellows, 2019), participants first learned the value of artificial stimuli ("fribbles"). In one condition, these values were determined by summing the values of individual attributes, while in another, values were only determined by the entire configuration of attributes. Individuals with VMF damage were as accurate as healthy and frontal controls when choosing between stimuli where value was defined by the individual elements, but made more errors when value was a configural property of the stimulus. In a potentially related finding, damage to the posteromedial OFC impaired performance in a category learning task where learning the category boundary required

integrating two stimulus dimensions (Schnyer et al., 2009).

Though VMF damage affects other aspects of how information is weighted and integrated in decisions, it does not alter the influence of attention on this process. People tend to look more at the option they ultimately choose, and Vaidya and Fellows (2015a) found that this link between fixations and choice was not altered by VMF damage. Instead, a VLSM analysis associated DMF damage with a reduced linkage between attention and choice.

Reward and attention

In a variety of different paradigms, VMF damage reduces sensitivity to reward cues (Aridan, Pelletier, Fellows, & Schonberg, 2019; Manohar & Husain, 2016; Pujara, Philippi, Motzkin, Baskaya, & Koenigs, 2016; Vaidya & Fellows, 2015b). Manohar and Husain (2016) found that individuals with medial prefrontal damage showed reduced speed in saccading to a rewarding target compared to healthy controls. VMF damage also reduces the effects of approach cues on preference. Images that are paired with an approach cue are liked better by healthy participants, but not by those with VMF damage (Aridan et al., 2019). Similarly, in a visual search task, healthy and frontal damaged controls experience a response time cost when a distractor is presented in a colour previously paired with reward, while those with VMF damage do not (Vaidya & Fellows, 2015b). VLSM analysis of 27 subjects with prefrontal damage localized this deficit to damage to gyrus rectus and posterior central OFC. Finally, consistent with this evidence for reduced reward sensitivity, individuals with bilateral VMF damage showed reduced ventral striatal responses to gain cues in the Monetary Incentive Delay task, relative to healthy participants (Pujara et al., 2016).

In a potentially related result, Koenigs and Tranel (2008) found that VMF damage reduced sensitivity to marketing cues. Specifically, healthy individuals prefer Coke to Pepsi when the drinks are labelled with the brand, and the reverse is true in a blind test; this difference was abolished by VMF damage. This reduced effect of brand cues on preferences might be analogous to the results above: with VMF damage, the conditioned rewarding aspects of the Coke brand is eliminated, and preferences are determined solely by the sensory evidence.

Anatomical specificity

VLSM evidence supports a strong role for the medial OFC and pregenual ACC in valuation. Damage to these regions has been linked to deficits in stimulus reversal learning, reduced sensitivity to reward cues, and altered weighting of stimulus attributes during valuation. Furthermore, the lateral OFC is critical for reward contingency learning, while the medial OFC is important for subjective awareness of values and choosing appropriately based on them. In contrast, the dorsomedial prefrontal cortex has been specifically linked to action reversal learning and to attentional influences on valuation. These results are all generally consistent with those of lesion studies in non-human primates.

General discussion

In this paper, we present a systematic review of human lesion studies of the ventromedial frontal lobe in the last two decades. Looking across 184 studies reviewed, there are many examples where the effects of VMF damage on cognition and behaviour are variable, or where evidence is mixed, tentative, or absent. However, there are also functions that are impacted reliably and consistently by VMF damage, as highlighted in the executive summaries for each of the above sections. We will now consider these reliable and consistent effects in the context of theories of VMF function.

One unified VMF function or many?

The multitude of cognitive domains in which the VMF is implicated has prompted many different theories regarding the functional specialization of this region. One account is that two distinct sub-regions within the VMF serve different specialized functions (Rudebeck et al., 2008). Specifically, according to this perspective, the OFC is important for reward learning, value representation and simple emotional responses, and the ACC/medial PFC is important for complex emotional and social responses. This notion is consistent with the anatomy of VMF, which contains two distinct, yet highly inter-connected, networks, the orbital sensory network and the medial network (Öngür & Price, 2000). The studies reviewed above do not provide strong evidence for, or against, this distinction, perhaps

because lesions in humans rarely dissociate these two networks cleanly.

A second, more radical, account proposes that all prefrontal regions work together with little functional specialization (Hunt & Hayden, 2017). In this view, all prefrontal areas are involved in hierarchical and distributed processing during complex behaviour like decision-making. Rather than any region being specialized for one function (e.g., VMPFC is for value), all regions simultaneously process the same variables and feed back to each other through recurrent connections, with the only specialization being the unique information that each region contribute to this process (e.g., VMPFC contributing limbic inputs). Generally, damage to the VMF does not cause stark deficits like those observed, for example, in visual agnosia or neglect, but rather graded and nuanced ones. For one example, lesions to the VMF do not impair the ability to recognize prototypical emotions but do impair the recognition of subtle emotional expressions (Heberlein et al., 2008; Jenkins et al., 2014; Tsuchida & Fellows, 2012; Willis et al., 2014; Wolf et al., 2014). For another example, VMF damage does not impair the ability to learn stimulus-reward associations when these are deterministic but does impair learning when these associations are probabilistic (Tsuchida et al., 2010; Camille et al., 2011). For another, though lesions to the VMF reliably lead to more inconsistent choices, the effect sizes are small (Camille et al., 2011; Fellows & Farah, 2007; Henri-Bhargava et al., 2012). All of these examples suggest that though VMF may contribute unique information to different psychological processes (e.g., emotional content in preference, Vaidya et al., 2017), other regions involved in these processes can mostly compensate when VMF is damaged.

Finally, there are several perspectives that ascribe a single purpose to the VMF, including (but not limited to) subjective value, affective regulation, representation of self and others, somatic markers, and affective meaning (Damasio, 1994; Delgado et al., 2016; Roy et al., 2012; Wallis, 2007). Each of these perspectives are supported by data, but often only within the domains that they most readily describe (e.g., decision-making, social cognition, emotion). In the next section, we will advance a perspective of VMF function aimed to account for findings across different cognitive domains and for the nuanced deficits observed within some domains.

States and schemas

Several lines of research from different areas of cognitive neuroscience have converged on the hypothesis that the VMF helps to represent the structure of the world. These representations are known as a "cognitive map" or "state space" in the fields of learning and decision-making (Schuck et al., 2018; Wilson et al., 2014) and as "schemas" in memory research (Ghosh & Gilboa, 2014; Preston & Eichenbaum, 2013; Schlichting & Preston, 2015). Though there are certainly differences, there are striking commonalities across the accounts offered in the memory and decision-making domains. Both accounts agree that the VMF is important for abstract, higher-order representations ("states" or "schemas") that enable inference of relationships that are not directly observed. The connectivity of the VMF uniquely positions this region to represent such higher order structures: OFC's connectivity to multiple sensory areas enables it to form an integrated representation of stimuli, and vmPFC's connectivity to medial temporal lobe structures, like hippocampus and entorhinal cortex, facilitates the integration of information from episodic and semantic memory.

The idea of cognitive maps can be traced to Tolman (1948). On one account of VMF function in learning and decision making, the OFC (including both lateral and medial areas) represents the state of the world, that is, all information that is relevant to the current decision (Niv, 2019; Schoenbaum et al., 2011; Schuck et al., 2018; Wilson et al., 2014). Thus, the OFC is necessary to (a) identify the aspects of the environment that are relevant to the subject, (b) represent partially observable information (i.e., variables that would require memory, like how much time has passed), and (c) infer the state of the world from observations. An OFC lesioned subject could still learn about states, but they would not be able to distinguish different states that are perceptually, though not conceptually, similar (e.g., in reversal learning where the stimuli look the same across states, but the reward contingencies have switched). The first function—identifying the relevant aspects of the environment during learning—is notably impaired in individuals with VMF lesions, for example they have trouble learning what the most relevant attribute of stimulus is (Noonan et al., 2017; Vaidya & Fellows, 2016). Individuals with VMF lesions also attend to and weight

attributes differently than healthy controls during decision-making (Fellows, 2006; Vaidya et al., 2017; Xia et al., 2015). To the second and third functions, many learning and decision-making tasks require inference and prediction of partially observable information (notably, the context, which must be inferred from past events or different elements in the current environment). For example, in the devaluation paradigm, the devaluation of the secondary reinforcer is not directly experienced and must be inferred from the devaluation of the primary reward. As another example, in reversal learning, representing a higher order "state" change (i.e., A is no longer the rewarding option; now B is), allows one to quickly detect and adjust to reversals. Other tasks that require inference and prediction are also impaired after VMF damage, such as integrating across multiple episodes when learning probabilistic reward associations (Camille et al., 2011; Tsuchida et al., 2010; Kovach et al., 2012) or across multiple attributes when learning the configural values or category boundaries (Pelletier & Fellows, 2019; Schnyer et al., 2009). The impact of these deficits on the representation of value could underlie the choice inconsistency and diminished motivation observed after VMF damage.

A related account of VMF function in memory research proposes that the VMF is necessary for the formation and encoding of schemas (Ghosh & Gilboa, 2014; Preston & Eichenbaum, 2013; Schlichting & Preston, 2015). Schemas are general, higher-order representations of the commonalities across multiple episodes, which can readily adapt to new information and support inferences to new situations. On this account, the VMF works with medial temporal lobe structures to abstract a schema from multiple individual episodes, bias memory retrieval to relevant schemas, and update schemas with new information (Schlichting & Preston, 2015; van Kesteren, Ruiter, Fernández, & Henson, 2012). The lesion evidence shows that the VMF is important for both naturalistic schematic representations (Ciaramelli et al., 2009; Spalding et al., 2015; Warren et al., 2014) and associative inferences (Koscik & Tranel, 2012; Spalding et al., 2018). This type of schematic representation can be useful for episodic memory and simulation. It has been proposed that the VMF acts sets the context for the retrieval of relevant elements during episodic construction (McCormick et al., 2018). A weakened ability to represent a coherent schematic framework would then lead to impoverished retrieval and coordination of episodic details for memory or imagination, especially when the scene is extended (Bertossi, Aleo et al., 2016; Bertossi, Tesini et al., 2016; De Luca et al., 2018). Finally, the concept of the self, a schematic framework organizing many aspects of an individual's identity, would also be weakened after VMF damage. Consistent with this, individuals with VMF damage do not show a self-referential bias in memory or imagination (Philippi et al., 2012; Verfaellie et al., 2019). Such a diminished representation of the self could also underlie the lack of self-awareness observed in individuals with VMF damage (Anderson et al., 2006; Barrash et al., 2011).

The related ideas of cognitive maps and schemas can also be extended the role of VMF in other domains. The recognition of emotion from subtle cues requires an inference regarding an at least partially hidden state (Heberlein et al., 2008; Jenkins et al., 2014; Tsuchida & Fellows, 2012; Willis et al., 2014; Wolf et al., 2014). The VMF, receiving information from the final stages of the ventral visual stream, could adjudicate between interpretations of emotional expressions, using contextual information or the subject's own emotional reaction. To further test this idea, future studies of emotion recognition could test whether contextual information affects the interpretation of subtle facial expressions in individuals with VMF lesions. Though the evidence for emotion regulation deficits after VMF damage is mixed, such a role for VMF also falls out of a cognitive map or schema framework—though there is neuroimaging evidence that the VMF is involved in grouping and separating fearful stimuli into different states (or schemas) for extinction (Gershman, Jones, Norman, Monfils, & Niv, 2013; Kalisch et al., 2006). When the extinction phase is introduced gradually—so that it is cognitively structured as contiguous with the initial fear conditioning rather than a separate phase—extinction is effective and enduring (in contrast, traditional, segregated periods of extinction leads to spontaneous fear response recovery).

Impaired schematic or state representations could also account for deficits in the social domain observed after VMF damage. When making moral judgments or social decisions, individuals with VMF damage de-emphasize context and instead focus on observable outcomes (Ciaramelli et al., 2012, 2013; Moretti et al., 2009; Moretto et al., 2013;

Young et al., 2010), suggesting that they may not be able to bring to bear the relevant social schema. Social inappropriateness, the inability to recognize faux pas, and the inability to generate valid solutions to social problems, could all be due to the breakdown of schemas for social norms (Pullen et al., 2006; Peters et al., 2017). The inability to generate counterfactuals or infer unobserved mental states could underlie what problems individuals with VMF damage have in other theory of mind tasks. A similar failure to generate unobserved counterfactual outcomes may also explain why individuals with VMF damage experience less regret and take more risks (Camille et al., 2004; Levens et al., 2014).

The idea that the VMF is critical for constructing, representing and updating states or schemas is a theoretically parsimonious account of many of the findings, across different domains, from the lesion studies reviewed above. Of course, many of these individual findings can also be explained by other perspectives on VMF function. In addition, some of the results in our systematic review are less easily reconciled with a cognitive map/schema framework, such as the changes in attention to reward, physiological reactions and personality that result from VMF damage. However, the cognitive map/schema viewpoint covers a wide range of findings, and has the additional benefit of producing testable new predictions. For example, studies could further test the hypothesis that the VMF is necessary for representing latent states using model-based learning (Daw, Gershman, Seymour, Dayan, & Dolan, 2011) or predictive inference tasks (McGuire, Nassar, Gold, & Kable, 2014). Similar, parallel tests could easily be developed to test the role of VMF in inferring unobserved variables in the social or emotional domains.

Future directions for lesion research

In terms of tasks for the future, the executive summaries for each of the domains point to many findings that need to be replicated and to many discrepancies that need to be resolved in a systematic, theory-driven manner. As the single most challenging aspect of lesion research is the difficulty in recruiting a large enough group of subjects, a greater degree of collaboration between research groups would be extremely beneficial to the future of cognitive neuroscience. Ideally, in the spirit of Open Science collaborations, researchers could share: (a) a standardized set of commonly agreed upon instruments and measures that can be used across research groups, and (b) lesions masks and behavioural results from these instruments, which would allow for pooled VLSM analyses. Such a "big data" approach would likely fast-track our understanding of the causal role of VMF (and other regions) in a multitude of domains.

Secondly, lesions studies should engage in more systematic investigations of neural networks, so as to move towards a more integrated understanding of the whole brain. Specifically, where possible, the same constructs should be tested in populations with damage to areas of the brain known to be interconnected with the VMF (e.g., hippocampus, amygdala, insula, ventral striatum, temporo-parietal junction, etc.). Some excellent and informative research studying memory and communication using this approach has elucidated the roles of interconnected brain regions in the same function (e.g., Gordon et al., 2014; Kurczek et al., 2015; Kurczek & Duff, 2011, 2012; Verfaellie et al., 2019). Moreover, more neuroimaging studies of individuals with VMF damage would help us better understand how such damage might induce functional and anatomical disruptions in networks interconnected with the VMF.

Conclusion

In this review, we have systematically and comprehensively surveyed the last twenty years of lesion research on the VMF, spanned multiple cognitive domains. We also discussed several theories of the function of the VMF and advocated for the idea that the VMF is critical for the formation of cognitive maps or schema. The value of lesion evidence cannot be overstated. A focus on causality, converging with other methods, is a powerful tool for scientific inquiry. We hope this review can be a resource to inform research and foster collaboration among both researchers who use the lesion method and those who use other methods, as well as a resource for clinicians and their patients to learn more about the sequalae of VMF damage.

Notes

1. "ventral frontal", "ventromedial frontal", "medial frontal", "orbital frontal", "orbito- frontal", "orbitofrontal", "ventral

prefrontal", "ventromedial prefrontal", "medial prefrontal", "orbital prefrontal", "ventral PFC", "ventromedial PFC", "medial PFC", "orbital PFC", "orbitoventral", "VMF", "VMPFC", "OFC", "OMPFC", "MPFC"

2. "alzheimer's disease", "Alzheimer disease", "dementia", "semantic dementia", "frontotemporal dementia", "epilepsy", "photic stimulation", "epilepsy, temporal lobe", "seizures", "schizophrenia", "major depressive", "parkinson disease", "addiction", "diabetes", "multiple sclerosis", "obsessive compulsive disorder", "case report", "review"

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