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Research report

Human ventromedial prefrontal lesions alter incentivisation by reward

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ABSTRACT

Although medial frontal brain regions are implicated in valuation of rewards, evidence from focal lesions to these areas is scant, with many conflicting results regarding motivation and affect, and no human studies specifically examining incentivisation by reward. Here, 19 patients with isolated, focal damage in ventral and medial prefrontal cortex were selected from a database of 453 individuals with subarachnoid haemorrhage. Using a speeded saccadic task based on the oculomotor capture paradigm, we manipulated the maximum reward available on each trial using an auditory incentive cue. Modulation of behaviour by motivation permitted quantification of reward sensitivity. At the group level, medial frontal damage was overall associated with significantly reduced effects of reward on invigorating saccadic velocity and autonomic (pupil) responses compared to age-matched, healthy controls. Crucially, however, some individuals instead showed abnormally strong incentivisation effects for vigour. *Increased* sensitivity to rewards within the lesion group correlated with damage in subgenual ventromedial prefrontal cortex (vmPFC) areas, which have recently become the target for deep brain stimulation (DBS) in depression. Lesion correlations with clinical apathy suggested that the apathy associated with prefrontal damage is in fact reduced by damage at those coordinates. *Reduced* reward sensitivity showed a trend to correlate with damage near nucleus accumbens. Lesions did not, on the other hand, influence reward sensitivity of cognitive control, as measured by distractibility. Thus, although medial frontal lesions may generally reduce reward sensitivity, damage to key subregions paradoxically protect from this effect.

1. Introduction

In recent years, investigations of cortical reward value representations have focused heavily on the role of ventromedial prefrontal cortex (vmPFC), sometimes also referred to as *medial* orbitofrontal cortex (Bartra, McGuire, & Kable, 2013; Hayes, Duncan, Xu, & Northoff, 2014; reviewed in Clithero & Rangel, 2014; Levy & Glimcher, 2012; Ruff & Fehr, 2014). But although vmPFC has been extensively implicated in computing reward value in human functional imaging

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studies, some investigators have contested this interpretation (O'Doherty, 2014; Stalnaker, Cooch, & Schoenbaum, 2015). Could the observed reward-related activations instead indicate a role in *regulating* reward signals – for example, in the basal ganglia – as a function of context? To date, animal evidence can be interpreted as weighing in favour of vmPFC playing a regulatory role, rather than its necessity for value-guided behaviour *per se* (Jo & Mizumori, 2015; Moorman & Aston-Jones, 2015; Rudebeck, Saunders, Prescott, Chau, & Murray, 2013; Schoenbaum, Takahashi, Liu, & McDannald, 2011). These two viewpoints make differing predictions regarding the effect of lesions. If vmPFC is responsible for computing value, then damage to this region might be expected to reduce the effect of reward on motivated behaviour. On the other hand, if its role were regulatory or modulatory, then damage to this region might paradoxically potentiate some of reward's direct effects.

Malfunctioning of the brain's value computation system has been proposed to underlie two distinct but related syndromes: depression and apathy (Alguacil & González-Martín, 2015; Eshel & Roiser, 2010; Hall, Milne, & Macqueen, 2014; Perry & Kramer, 2015; Rochat et al., 2013; Sinha, Manohar, & Husain, 2013; Whitton, Treadway, & Pizzagalli, 2015). These behavioural conditions, which occur frequently across a range of brain disorders, have been characterised either as blunted reward sensitivity, or aberrant regulation of reward value (Cipriani, Lucetti, Danti, & Nuti, 2014; Foussias, Agid, Fervaha, & Remington, 2014; Hellmann-Regen et al., 2013; Marin & Wilkosz, 2005). Intriguingly, neuroimaging studies have highlighted abnormal vmPFC activity in both these disorders (Alexopoulos et al., 2013; Drevets, Price, & Furey, 2008; Koenigs & Grafman, 2009; Ubl et al., 2015), and some investigations have even reported that major depression can be successfully alleviated by surgical lesions or deep brain stimulation (DBS) of posterior vmPFC white matter (Bridges et al., 1994; Johansen-Berg et al., 2008; Mayberg et al., 2005; Moreines, McClintock, Kelley, Holtzheimer, & Mayberg, 2014; Schlaepfer et al., 2007). Taken together, these findings suggest that inappropriate or dysregulated control over reward could characterise affective or motivational disorders. Establishing a link between motivational disorders and human vmPFC damage could therefore provide stronger causal evidence for this region's role.

Studies on human focal lesions involving vmPFC would provide an ideal opportunity to test the role of this region in reward processing. However, focal damage to this region of the brain is relatively uncommon, and those studies that have been conducted have often been based on small numbers of participants. Moreover, reported effects following lesions are heterogeneous and often seemingly conflicting. For example, both apathy as well as impulsivity have been documented (Berlin, Rolls, & Kischka, 2004; Jouvent et al., 2011; Lhermitte, 1986); while blunted affect and emotional lability are frequent (Angrilli, Palomba, Cantagallo, Maietti, & Stegagno, 1999; Beer, Heerey, Keltner, Scabini, & Knight, 2003; Ghaffar, Chamelian, & Feinstein, 2008; Kim & Choi-Kwon, 2000). Furthermore, different studies have suggested either a predisposition to or even protection from depression (Ellenbogen, Hurford, Liebeskind, Neimark, & Weiss, 2005; Kim & Choi-Kwon, 2000; Koenigs & Grafman, 2009; Koenigs et al., 2008; MacFall, Payne, Provenzale, & Krishnan, 2001). From this evidence it is difficult to conclude that lesions to human vmPFC influence reward processing, or impact on motivation. It is possible that motivation in different aspects of behaviour may be differentially affected. Importantly, the question remains open as to whether reward sensitivity would be blunted or increased by damage to this region.

To better characterise effects of lesions, cognitive tasks that attempt to tap specific processes have been employed, e.g., to demonstrate disturbed decision-making following vmPFC lesions (Fellows & Farah, 2005; Gläscher et al., 2012; Levens et al., 2014), though even these have been inconsistent (Manes et al., 2002). Specifically, vmPFC lesions can lead to suboptimal or higher betting in risk-related decisions (Clark et al., 2008; Levens et al., 2014; Studer, Manes, Humphreys, Robbins, & Clark, 2015), coupled with altered autonomic anticipatory responses (Bechara, Damasio, Tranel, & Damasio, 2005). vmPFC patients also exhibit altered reversal learning of stimulus-reward associations (Fellows & Farah, 2003; Hornak et al., 2004; Tsuchida, Doll, & Fellows, 2010). All these might be consequences of a more pervasive disorder of *evaluation*, as manifest by abnormal and self-inconsistent preferences (Fellows & Farah, 2007; Koenigs & Tranel, 2008). But surprisingly, to the best of our knowledge, there is no study that has directly examined the effect of vmPFC lesions on *incentivisation by reward value* in humans.

Here, our aim was to test the specific role of vmPFC in using value to incentivise action. To do this, we adapted the oculomotor capture task, which has previously provided detailed insights into the automatic effects of reward (Anderson & Yantis, 2012; Hickey, Chelazzi, & Theeuwes, 2011; Jazbec et al., 2006; Le Pelley, Pearson, Griffiths, & Beesley, 2015). We used this paradigm in patients with focal damage in the anterior cerebral artery (ACA) territory, following subarachnoid haemorrhage. The task is a simplified variant of the oculomotor capture paradigm (Theeuwes, Kramer, Hahn, & Irwin, 1998; Van der Stigchel, van Koningsbruggen, Nijboer, List, & Rafal, 2012), in which participants have to exert a degree of cognitive control. Similar to an anti-saccade task, participants must look away from a visually salient onset. Crucially, to probe how *motivation by reward incentives* influences behaviour, we varied the amount of money that could be won for each saccade, on a trial-by-trial basis, using an auditory precue. Monetary incentive cues have recently been shown to modulate the velocity of saccades on this task (Manohar et al., 2015). In addition, we assessed autonomic responses to reward on offer by measuring pupillary dilatation. Motivational effects of reward were quantified by saccadic velocity (response vigour), pupillary dilatation (autonomic response) and oculomotor capture (cognitive control) as a function of different reward values. We predicted that vmPFC lesions might alter the effect of reward on these measures.

Our aim here was not to define all brain regions involved in processing reward but to investigate specifically whether medial prefrontal cortical lesions have an impact on reward sensitivity. We used hypothesis-based, region of interest (ROI) predictions as well as whole brain voxel-based lesion mapping specifically to probe regions *within* medial PFC, which when lesioned, lead to alterations in reward sensitivity.