Social attention and the ventromedial prefrontal cortex

Imagine looking out over the patrons in a restaurant as one of them looks up from their plate of food and makes eye contact with you. The change in the visual image on your retina is miniscule, yet the knowledge gained is great. A tiny change in the movements of another person's eyes lets you know instantly that they are looking at you, know that you are also looking at them, and feel a particular emotion or have a particular intention. In this issue of *Brain*, Wolf *et al*. (2014) describe three patients with focal lesions of the ventromedial prefrontal cortex (vmPFC) who show strikingly atypical patterns of fixation onto faces: they do not look at a person's eyes, with implications for social decision-making.

The eye region of faces is salient not only because it tells us where somebody else is directing their attention, but also because it informs us of their emotional state (the muscles around the eyes contribute substantially to certain emotional facial expressions, most particularly fear). Deficits in our ability to process this information may underlie aspects of paranoid schizophrenia (feeling as though somebody is watching you all the time) as well as autism spectrum disorders (where diminished eye contact is associated with social disengagement; Fig. 1). The ability to use our perception of another person's gaze to guide our own attention emerges during specific stages of early development, and some aspects of this ability may be unique to humans (although dogs are also quite good at figuring out social attention signals). To understand these different facets of social attention, it is a high priority to elucidate the neural substrates involved.

The data obtained by Wolf *et al*. from the three patients with focal vmPFC lesions are intriguing for two reasons: first, they pose a challenge with regards to their incorporation into leading

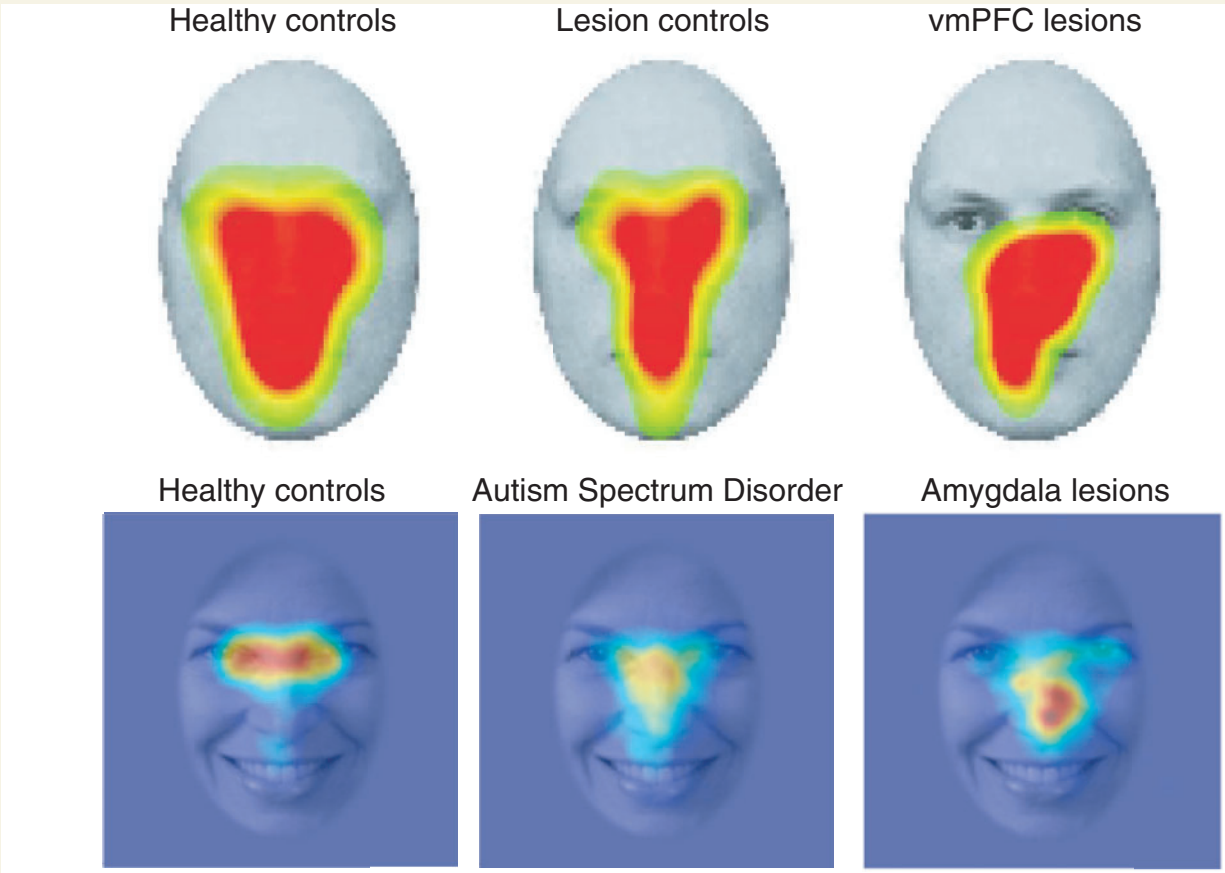

Figure 1 Failing to look at the eyes. Shown in each image are the regions of a face at which different groups of subjects look, as measured using eye-tracking. The hottest colours (red regions) denote those regions of the face where people look the most. Whereas this corresponds to the eye region of the face in healthy controls (*far left*), it is abnormal in certain clinical populations, including individuals with lesions of the vmPFC (*top right*) or amygdala (*bottom right*) and individuals with autism spectrum disorder (*bottom centre*) *Top row*: from Wolf *et al*. 2014. *Bottom row*: data from Michael Spezio, Daniel Kennedy, Ralph Adolphs. All images represent spatially smoothed data averaged across multiple fixations, multiple stimuli and multiple subjects within the indicated group.

accounts of the functions of this brain region in decision-making; and second, they link the vmPFC to another brain structure, the amygdala, damage to which seems to produce very similar impairments.

The vmPFC has long been implicated in social behaviour, emotion and decision-making (Damasio, 1994), and is currently under intense investigation in relation to reward learning. Although there is some debate regarding whether vmPFC itself encodes the value of rewards (Jones *et al*., 2012), everyone seems to agree that it plays a key role in a particular type of decision-making that requires us to think about the consequences of our actions. This is variously reflected in 'goal-directed' or 'model-based' forms of reward learning, or an ability to imagine what will happen in one's autobiographical future. All of these abilities activate the vmPFC in neuroimaging studies, and all are compromised by lesions to it; all are generally thought to be effortful and to diminish (and become more habitual) with practice.

Wolf *et al.* provide data that seem to argue for a different level of processing: the vmPFC may also be important for the early allocation of attention, required to select stimuli for further processing. This idea is consistent with evidence that top–down signals from the prefrontal cortex may guide visual imagery and visual search. Remarkably, strikingly similar findings are available for one other brain structure: the amygdala. Like the vmPFC, the amygdala is involved in social behaviour, emotion and decision-making (Murray, 2007). The amygdala was also recently shown to play an attentional role that influences how we fixate eyes within faces (Adolphs *et al.*, 2005; Fig. 1).

How could impaired visual attention relate to impaired social behaviour and decision-making? If you do not pay proper attention to a face, you will not recognize its emotions, hence you will show impaired social behaviour, and you will have difficulty making social decisions. It may be that attention and decision-making simply rely on slightly different regions, or subpopulations of neurons, within the vmPFC. But it may also be that they reflect a more unitary function, just implemented at different points in time. Perhaps initial attentional selection determines whereabouts on the face we look first, and information about the value and significance of the facial features sampled then, in turn, influences where we look next. Exactly how this plays out in time, and how it depends on relative roles of the vmPFC and the amygdala, is a complex question that only electrophysiological methods can resolve (for an example in the case of reward learning, see Morrison *et al*., 2011). Similarly, considerably more work would be needed to circumscribe the deficit: is it specific to faces? To social stimuli? To complex visual stimuli? Additional experiments that would be informative in this regard are ones that measure fixations onto a larger range of visual stimuli, and under a range of task demands (e.g. spontaneous viewing, perceptual judgment or directed visual search).

There are plenty of caveats for how best to interpret the study by Wolf *et al*., caveats for which the authors themselves provide an admirably clear discussion in their paper. The lesions of course are not specific to a single Brodmann area, nor even to grey matter; the sample size is small; and no doubt there have been some plastic changes since the onset of the lesion (an issue of particular interest given the work on developmental-onset lesions of the vmPFC, e.g. Taber-Thomas *et al*., 2014). It is often unclear how best to establish the statistical reliability of findings from such small samples. Sometimes, they can be treated as multiple case studies and compared against a small group of suitably matched comparison subjects (often involving statistical tests that correct for small samples, such as those that John Crawford has long championed). Alternatively, they could be treated as a (very) small group of $n = 3$ (the approach chosen by Wolf *et al.*). There is also something to be said for refraining from assigning any sort of statistical significance to the findings altogether, and simply reporting the (typically large) effect in detail (Cumming, 2014), a quantitative foundation on which similar future studies can then build.

Perhaps in good part for reasons of statistical reliability, instructions for aspiring authors in *Brain* make a point of noting that case studies are discouraged, yet the present study offers what essentially amounts to three case studies. As someone who has authored his share of case studies, it will come as no surprise that I am rather fond of this category, for several reasons. The primary reason is simple: if you are going to publish a case study, your story had better be interesting and your effect size large. That is the case also with the data of Wolf *et al*.: not only does each of the three vmPFC patients show a strongly atypical eye-tracking pattern to faces, but, especially for fearful faces, the atypicality is remarkably consistent across the three patients. Weaker and less reliable effects would require larger samples to detect them. A second reason for my fondness for case studies is that they generally are about deficits (e.g. due to lesions, as in the present paper), and hence generally admit of a stronger causal link between brain and psychology than do the much more numerous neuroimaging studies of healthy individuals. It is worth noting that the title of the paper by Wolf *et al*., strictly speaking, does not follow from their findings: impaired visual attention following vmPFC lesions does not imply that the vmPFC therefore normally mediates this process. Showing that the vmPFC mediates the process would be much more difficult and would require experimentally replaying the pattern of activity normally seen in a healthy vmPFC to see if this engaged visual attention (something now becoming possible with optogenetic tools in rodents, but currently impossible in humans). Of course, neither lesions nor optogenetics would show that the process is 'in' the vmPFC, or that the vmPFC is sufficient for social attention, since the vmPFC is connected with the rest of the brain.

Which brings us to the final consideration of how best to interpret the findings of Wolf *et al*. We know that lesions in either vmPFC or in the amygdala produce similar deficits in social attention to the eyes in faces. Might lesions in one of these structures produce abnormal blood oxygenation level-dependent (BOLD) functional MRI signals in the other? We once carried out an experiment showing abnormal signals in the prefrontal cortex in patients who had bilateral amygdala lesions (Hampton *et al*., 2007), but the converse experiment remains to be done. Even more interesting are those cases or trials in which, despite their lesion, patients exhibit relatively normal performance—an occasional event that should not be dismissed as 'variability' or 'noise' as it constitutes valuable data in its own right. Lesions to the amygdala, for instance, can sometimes leave a relatively spared ability to recognize emotional facial expressions,

but in these cases, there is an explanation that can be revealed with functional MRI: other regions of the brain seem to compensate (Becker *et al*., 2012). The extension to a whole-brain field of view (one of the undisputed virtues of functional MRI) will also provide a stronger link to psychiatric disorders in which vmPFC and/or amygdala are thought to be dysfunctional. Wolf *et al*. have thus provided a study that also suggests the experiment they should run next: put these three patients into a scanner and find out how their lesions influence processing in the rest of the brain.

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Voltage-gated sodium channel mutations and painful neuropathy: $Na_v1.9$ joins the family

In its simplest terms neuropathic pain arises as a consequence of hyperexcitability within the somatosensory nervous system. It is not surprising therefore that voltage-gated sodium channels (VGSCs), with their key role in regulating neuronal excitability, have come to the fore as pathophysiological factors in human neuropathic pain states. Not only can mutations in these ion channels lead to altered impulse generation/conduction in sensory neurons but they may also lead to degeneration of axon terminals. The VGSC family of proteins has nine members, of which $Na_v1.7$, $Na_v1.8$ and $Na_v1.9$ (encoded by the genes *SCN9A*, *SCN 10A* and *SCN 11A*, respectively) are preferentially expressed in peripheral neurons (Eijkelkamp *et al*., 2012). While gain of function variants of $Na_v1.7$ and $Na_v1.8$ have previously been reported in patients with painful peripheral neuropathy, in this issue of *Brain*, Huang *et al*. (2014) present the first evidence for a causative role of missense mutations in $Na_v1.9$ in painful neuropathy.

The biophysical properties and distribution of $Na_v1.7$, $Na_v1.8$ and $Na_v1.9$ regulate key aspects of nociceptor function. $Na_v1.7$ is likely to be an important determinant of threshold for excitation in nociceptor terminals and may also regulate neurotransmitter release at the central terminals of nociceptors. Homozygous, loss of function mutations in $Na_v1.7$ result in congenital inability to experience pain and anosmia in man, whereas heterozygous gain of function mutations have been linked to the distinct clinical pain syndromes of inherited erythromelalgia (IEM: pain and erythema exacerbated by warming), paroxysmal extreme pain disorder (PEPD: proximal pain and autonomic features in ocular/mandibular and sacral regions), and small fibre neuropathy [SFN: degeneration of small diameter sensory and autonomic axons usually presenting with severe burning pain in extremities (Persson *et al*., 2013)]. $Na_v1.8$ carries most of the current underlying the depolarizing phase of the action potential in dorsal root ganglion neurons and so is critical for transmission of action potentials and repetitive firing. Heterozygous gain of function mutations in $Na_v1.8$ have recently been linked to small fibre neuropathy (Faber *et al*., 2012).

So what of Nav1.9 (encoded by the gene *SCN11A*), which is the focus of the report by Huang *et al*. in this issue of *Brain*? $Na_v1.9$ is expressed particularly by small diameter dorsal root ganglion cells, the majority of which will be nociceptors (Dib-Hajj