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Ventromedial frontal lobe damage affects interpretation, not exploration, of emotional facial expressions

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Abstract

Recognizing and distinguishing the emotional states of those around us is crucial for adaptive social behavior. Previous work has shown that damage to the ventromedial frontal lobe (VMF) impairs recognition of subtle emotional facial expressions and affects fixation patterns to face stimuli. However, whether this relates to deficits in acquiring or interpreting facial expression information remains unclear. We tested 37 patients with frontal lobe damage, including 17 subjects with VMF lesions, in a series of emotion recognition tasks with different gaze manipulations. Subjects were asked to rate neutral, subtle and extreme emotional expressions while freely examining faces, while instructed to look only at the eyes, and in a gaze-contingent condition that required top-down direction of eye movements to reveal the stimulus. People with VMF damage were worse at detecting subtle disgust during free viewing and confused extreme emotional expressions more than healthy controls. However, fixation patterns did not differ systematically between groups during free or gaze-contingent viewing conditions. Moreover, instruction to fixate only the eyes did not improve the performance of VMF damaged subjects. These data argue that VMF is not necessary for normal fixations to emotional face stimuli, and that impairments in emotion recognition after VMF damage do not stem from impaired information gathering, as indexed by patterns of fixation.

Introduction

Recognizing emotions in others is critical to navigating social interactions. Doing so requires reading meaning from facial expressions, inferring internal state from signals like furrowed brows or eyes that ‘light up.’ Deficits in recognizing emotional facial expressions are found in many neuropsychiatric disorders, including autism and schizophrenia (Kohler, Walker, Martin, Healey, & Moberg, 2010; Uljarevic & Hamilton, 2013), hindering interpersonal interaction. Defining the neural circuits underlying this ability is fundamental to understanding how social deficits arise in these clinical populations, which in turn could improve diagnosis and guide treatment.

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Studies of subjects with focal lesions have helped establish some of the brain regions that are crucial for emotion recognition. Lesions of the temporo-parietal and ventral visual cortex in the right hemisphere, and subcortical lesions of the amygdala, have been found to affect recognition of extreme emotional expressions like those in the classic stimulus set from Ekman and Friesen (1976) (Adolphs, Damasio, Tranel, Cooper, & Damasio, 2000; Adolphs, Damasio, Tranel, & Damasio, 1996; Adolphs, Tranel, Damasio, & Damasio, 1994).

In several clinical populations, such as autism and schizophrenia, deficits in facial emotion recognition have been associated with abnormal gaze patterns to face stimuli (Jones & Klin, 2013; Klin, Jones, Schultz, Volkmar, & Cohen, 2002; Pelphrey et al., 2002; Streit, Wolwer, & Gaebel, 1997). These findings have been taken as evidence that emotion recognition deficits frequently arise from impairment in seeking out or focusing attention on emotionally informative features of the face, in particular, the eyes (Baron-Cohen, Wheelwright, & Jolliffe, 1997). This argument is further supported by evidence that healthy individuals use visual information gleaned from the eye region to recognize and discriminate several emotional categories (Peterson & Eckstein, 2012; Smith, Cottrell, Gosselin, & Schyns, 2005; Vaidya, Jin, & Fellows, 2014). Focal lesions of the amygdala have been shown to disrupt fear recognition by affecting fixations to face stimuli. Much of this evidence is from studies of a single patient, SM, a woman with selective, bilateral lesions of the amygdala and profound deficits in recognizing fearful expressions (Adolphs et al., 1994). SM's fixations to faces were found to be highly disorganized. However, when instructed to look at the eyes, SM's fear recognition deficit resolved (Adolphs et al., 2005). To test if SM's disorganized fixation patterns were the consequence of a failure in top-down control of gaze, Kennedy and Adolphs (2010) asked SM to view faces through a gaze-contingent window, forcing her to use a top-down strategy to guide eye movements. Under these conditions, SM made fixations primarily to the eyes, suggesting that the amygdala is necessary for bottom-up orienting of fixations to face stimuli, but not goal-directed, top-down exploration.

The literature reporting the effects of damage to the ventromedial frontal lobe (VMF: encompassing orbitofrontal (OFC) and ventromedial prefrontal (vmPFC)) on emotion recognition from extreme, prototypical face stimuli is inconsistent (Hornak et al., 2003; Hornak, Rolls, & Wade, 1996). Such lesions seem to more reliably disrupt detection of emotion presented as subtle morphs between prototypical emotional (except happy) and neutral faces (Heberlein, Padon, Gillihan, Farah, & Fellows, 2008; Jenkins et al., 2014; Tsuchida & Fellows, 2012). Robust connections between the amygdala and OFC (Barbas, 2007; Price, 2007), and co-activation of amygdala and vmPFC in fMRI studies of emotional expression processing (Fusar-Poli et al., 2009) add to the evidence that these regions are part of a functional circuit for processing emotional faces. Two recent neuropsychological studies have suggested that emotion recognition deficits associated with VMF damage arise from a failure to look to the eyes, much like SM. Wolf, Philippi, Motzkin, Baskaya, and Koenigs (2014) found that three subjects with large bilateral VMF lesions had reduced fixations to the eye region of extreme emotional faces. In a follow-up study, this group showed that instructions to look at the eyes improved the performance of seven subjects with VMF damage in recognizing moderate emotional expressions (Wolf, Pujara, Baskaya, & Koenigs, 2016). However, in both these studies emotion recognition impairments were modest, and fixations to the eyes were only reduced in some conditions. It remains unclear whether

emotion recognition deficits following VMF damage are a consequence of a failure to seek out informative facial features, and what role this region plays in controlling fixation behavior and visual attention. For example, VMF damage could affect a top-down strategic process that guides attention to informative features, or the bottom-up process that seems to be disrupted after amygdala damage.

The aim of the current study was to test whether VMF plays a necessary role in adaptively directing visual fixations to faces, and detecting and discriminating between emotional expressions. In a study of healthy young subjects, we found that fixations to the eye region predicted recognition of subtle afraid and disgusted emotional expressions, but not subtle happiness or extreme emotions (Vaidya et al., 2014). Based on this work, we anticipated that VMF-damaged patients would show reduced fixations to the eye region, and would have deficits in detecting subtle, but not extreme or happy emotions. As a secondary aim, we sought to characterize the mechanism of putative emotion recognition impairment in these patients by testing how instruction to fixate the eyes affected emotion recognition performance, and how requiring subjects to view the stimulus through a gaze-contingent window affected fixation patterns.

Methods

Subjects

Subjects with frontal lobe damage ($N = 41$) were recruited from the Cognitive Neuroscience Research Registry at McGill University (Fellows, Stark, Berg, & Chatterjee, 2008). They were eligible if they had a fixed lesion (from ischemic or hemorrhagic stroke or tumour resection) primarily affecting the frontal lobes. Four subjects were excluded from the analysis: one failed to keep track of the emotional labels between blocks and testing was stopped early, two others had poor quality eye-tracking data due to heavily scratched glasses in one case, and incessant blinking in another. All three had damage sparing the ventromedial frontal lobe. One subject was excluded because the extent of her lesion could not be characterized with confidence due to residual tumor.

Subjects with frontal lobe damage were tested a minimum of 5 months after injury (median, 4.8 years; range: 5 months to 48 years). Fourteen were taking one or more psychoactive medications: 10 were taking anticonvulsants, 5 were taking anti-depressants. There was no significant difference in the frequency of psychoactive medication use between frontal lobe damaged groups (Chi-square test of independence: $\chi^2(2) = 1.08$, $P = 0.6$).

Twenty-seven age- and education-matched healthy control subjects were recruited through local advertisement in Montreal. One control subject fell asleep during the experiment and was excluded, leaving 26 healthy controls in the analysis. All healthy controls were free of neurological or psychiatric disease and were not taking any psychoactive drugs. All scored 27 or higher (mean score 28.4/30, SD 1.3) on the Montreal Cognitive Assessment (Nasreddine et al., 2005).

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

Lesion analysis

Individual lesions were traced from the most recent clinical computed tomography or magnetic resonance imaging onto the standard Montreal Neurological Institute (MNI) brain using MRICro software (Rorden & Brett, 2000) (freely available at www.mccauslandcenter.sc.edu/mricro/) by a neurologist experienced in imaging analysis and blind to task performance. A related software tool (MRICron) was used to generate lesion overlap images and estimate lesion volumes. Patients were separated into a VMF group, and a frontal control (FC) group consisting of patients with frontal lobe damage sparing VMF, by the same neurologist. The grouping of subjects conformed to broad anatomical frontal lobe subdivisions commonly used in neuropsychological studies (Stuss et al., 2005). One patient in the FC group had a second lesion in the parietal lobe, and one patient in the VMF group had an additional lesion in the parietal white matter. FC lesions were due to tumor resection in 12 cases, ischemic stroke in five cases, hemorrhagic stroke in two cases and aneurysm rupture in one case. Lesions affecting VMF were attributable to tumor resection in 13 cases, aneurysm rupture in three cases, and hemorrhagic stroke in one case.

Three subjects in the VMF group had bilateral damage affecting this region due to tumor resection in two cases, and aneurysm rupture in one. The causes and patterns of damage for these three subjects are similar to that of the subjects studied in Wolf et al. (2014), who looked at the eyes less when examining facial expressions. While these subjects were included in the VMF group, in keeping with the *a priori* study design, we also assessed their performance separately in an effort to replicate the Wolf et al. observations. Figure 1 shows the lesion overlap in the FC and entire VMF group and the three subjects with bilateral VMF damage separately.

Neuropsychological screening

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

Apparatus

All experimental tests were programmed using E-Prime 1.2 (Psychology Software Tools, Inc., Pittsburgh, PA, USA). Subjects' heads were stabilized using a headrest and stimuli were presented on a 19-inch monitor (Dell Inc., Round Rock, TX, USA) positioned approximately 57 cm from their eyes. Monocular recordings of the movement of each

subject's dominant eye were acquired at 1000 Hz using an Eyelink 1000 system with a desk-mounted camera (SR Research Ltd., Mississauga, Ontario, Canada).

Stimuli

Face stimuli were selected from the Karolinska Directed Emotional Faces stimulus set (Lundqvist, Flykt, & Olman, 1998). These included neutral and extreme emotional expressions from 8 actors, 4 men and 4 women. Subtle emotional stimuli were created by morphing images of extreme and neutral emotional faces for each actor. All images were converted to grayscale, corrected for mean luminance and cropped to fit a 10.7 by 15.0° oval. A detailed description of the creation of these stimuli can be found in Vaidya et al. (2014).

Facial features for each stimulus were defined as areas of interest (AOIs) for analysis purposes. These areas were manually defined for each stimulus using horizontal bands that parcellated faces into forehead (top of stimulus to start of eye-brows), eyebrows (top of eye-brows to upper orbit), eyes (upper orbit to bottom orbit), nose and cheeks (from bottom of orbit to tip of nose), mouth (from tip of nose to bottom of lower lip), and chin (from bottom of lower lip to bottom of stimulus).

Heat maps for each subject were created by mapping dwell times (i.e. fixation durations) at fixation locations across all stimuli and conditions onto a 180×240 matrix, matching the pixel dimensions of the face stimulus. This matrix was then smoothed using a 30×30 two-dimensional lowpass Gaussian filter with a standard deviation of 5 and normalized to the range of dwell times after smoothing. The images in this manuscript were created by averaging these matrices across subjects in each group.

Free viewing

The general design of this experiment was very similar to past emotion rating tasks in other neuropsychological studies by our group and others (Adolphs & Tranel, 2004; Heberlein et al., 2008; Tsuchida & Fellows, 2012; Vaidya et al., 2014). Subjects were asked to judge the extent to which faces showed a different target emotion in each block. These target emotions were fear, disgust and happiness, selected from the six basic Ekman emotions (Ekman & Friesen, 1971), because of their semantic and perceptual dissimilarity (Dailey, Cottrell, Padgett, & Adolphs, 2002). Within each block, subjects were presented with faces displaying neutral, subtle, or extreme emotional expression from these same three target categories. Subjects judged all stimuli for each target emotion (i.e. subjects judged the same expression for fear, disgust and happiness). There were 3 blocks of 36 trials, 12 trials with neutral faces and four trials for each emotional display at subtle and extreme degrees.

At the beginning of the experiment, subjects were presented with four practice trials asking them to judge how afraid a series of faces were. These trials included, in order, an extremely afraid face, a neutral face, a subtly afraid face and an extremely happy face. This practice phase was intended to familiarize subjects with the range of expressions in this task and the task procedure. All faces in this practice were the same actor, and not included in the main experiment.

Before beginning the task, subjects completed a 9-point eye-tracker calibration and validation sequence covering a 22 by 17° area. On each trial, subjects had to hold fixation for 500 ms on a cross randomly presented on the left or right side of the screen on the horizontal meridian, 7.1° from the center. Thus, subjects always had to saccade away from this cross to fixate the face stimulus, ensuring that the subject was not looking directly at the face stimulus when it first appeared. This process also served to ensure the quality of calibration throughout the test: Failure to maintain fixation in a 1.7 by 1.8° box around the fixation cross would cause the fixation slide to repeat. After four consecutive failures, the eye-tracker would be recalibrated.

On each trial, once the criterion for fixation was met, subjects were presented with a central face stimulus. Subjects were allowed to freely inspect the stimulus for 2000 ms from the time gaze crossed over the border of the stimulus. The face was then replaced with a 10-point Likert scale with a prompt asking subjects to judge the sub-block target emotion (e.g. 'How HAPPY was the face?') and written labels below the numbers on the scale to provide context for subjects' ratings. The scale ranged from 1 ('Very slightly or not at all'), 3 ('A little'), 5 ('Moderately'), 8 ('Quite a bit') and 10 ('Extremely'). Subjects would then choose a rating using the mouse.

Gaze contingent viewing

In the gaze contingent viewing condition, subjects completed one block where they were asked to judge faces for fear while viewing stimuli through a 3.6° diameter circular aperture that appeared at the location of subjects' fixation. Before beginning this block, subjects practiced using this aperture by first searching for small pictures of animals hidden on-screen, and then examining facial expressions from the same four practice trials used in the free viewing block, only now with the gaze-contingent aperture. As in the free viewing block, subjects were required to first hold fixation at a peripheral fixation cross at the start of each trial, and face stimuli appeared in the same location at the center of the screen once the criterion for a fixation was met. The number of trials and balance of neutral, subtle and extreme emotional stimuli for each emotional display was the same as single block in the free viewing condition. The stimuli in this second block were all different from the free viewing condition to avoid the possibility that subjects might form their ratings based on previous judgments after recognizing faces from partial information.

Instructed viewing

Subjects were once again asked to judge how afraid a series of faces appeared, but now with the explicit written and verbal instruction to only look at the eyes of the face and no other features. These instructions were presented in written form, and reiterated by the experimenter several times before the start of the block. Aside from these instructions, the design of these blocks was identical to the sub-blocks of the free-viewing condition. The face stimuli in these conditions included a mix of stimuli from the first two blocks.

Some frontal lobe damaged subjects failed to maintain fixation to the eyes. This failure to comply with instructions made it difficult to interpret the behavior of these subjects in this condition, as it was unclear if these subjects had difficulty maintaining fixation to the eyes,

were ignoring instructions, or forgot the instructions during the task. As the main purpose of this manipulation was to test how exclusive fixation of the eyes affected recognition performance, these subjects were excluded from analysis of these data. Subjects were excluded if the proportion of time spent on the eyes across trials was three standard deviations less than the average proportion of time spent on the eye region by control subjects (i.e. less than 55.8% of total dwell time). With this criterion, four VMF subjects and two FC subjects were excluded. Although these subjects failed to follow instructions to fixate the eyes, measures of emotion rating sensitivity and specificity for these four VMF damaged subjects were not significantly different from the rest of the VMF group in this instructed viewing condition (between subjects t-tests: $t(17) = 0.82$, $p = 0.4$).

Eye-tracking analysis

Fixations were defined using the online parser of the Eyelink 1000: saccades were identified using a velocity threshold of 30° per second, an acceleration threshold of 8000° per second squared and a distance threshold of more than 0.15° . This same parser also automatically rejected blinks. In-house written Matlab (Mathworks, Natick, MA, USA) scripts were used to determine the location of fixations and extract the data for analysis.

Statistical analysis

As in Tsuchida and Fellows (2012), raw ratings of emotional faces were transformed into proportional difference (pD) scores to account for baseline differences in emotional ratings as well as subject-wise differences in the utilization of the rating scale. These scores were calculated by subtracting the average rating of neutral faces from the ratings of emotional faces for each target emotion in a block. This difference was then divided by the overall rating range within a block (i.e. the maximum rating minus the minimum rating). These pD scores were then compared between groups and across conditions using Mixed-Measures ANOVAs.

An index of rating specificity was calculated based on these pD scores, also following the method used in Tsuchida and Fellows (2012). This index was calculated by subtracting the mean pD scores for non-target emotional faces from the pD score of the target emotion in each block. As this measure was strongly related to pD scores for the target emotions ($r^2(61) = 0.48$, $P < 0.0001$), this measure was residualized based on these linear correlations. One-way ANOVAs were then used to compare these residual scores between groups.

Given that fixation data are compositional, an isometric logratio (ILR) transformation was performed on the frequency of fixations and the proportion of dwell time on face AOIs. This transformation corrects for the dependencies between compositional data points, permitting the use of standard multivariate analyses (Aitchison, 2003; Schilling, Oberdick, & Schilling, 2012). Effects of group status on the transformed fixation data were analyzed using one-way MANOVAs. Significant effects were followed up with one-way ANOVAs. Fixation data were also analyzed with more conventional tests on the raw, untransformed proportion data using mixed-measures ANOVAs. Post-hoc tests were carried out using t-tests with the alpha level corrected for multiple comparisons using the Bonferroni method.

Relationships between behavioral measures (pD scores and the specificity index) were carried out using multiple linear regression analyses, where the ILR transformed fixations to the eyes, nose and mouth were predictor items and behavioral measures were treated as outcomes.

Heat maps were compared between groups using massive univariate t-tests across all pixels within the oval face stimuli. Permutation tests were used to generate a null distribution of test statistics to find a criterion for statistical significance correcting for multiple comparisons by randomly shuffled group labels (Nichols & Holmes, 2002), and testing if any t-statistics exceeded the 97.5% cutoff of the distribution of the maximum and minimum statistics ($\alpha = 0.05$, two-tailed).

Voxel-based lesion symptom mapping

The Non-Parametric Mapping (NPM, version May 2, 2016) software (freely available at www.mccauslandcenter.sc.edu/mricro/npm/) was used for voxel-based lesion symptom mapping (VLSM) analysis. Voxel-wise comparisons between subjects were carried out using non-parametric Brunner-Munzel (BM) tests (Brunner & Munzel, 2000) in all voxels where there were three or more patients with lesion damage. To control for multiple comparisons, a null distribution of BM Z-scores was calculated from the same dataset using permutation tests (3000 permutations). Images of the results of this analysis were created using the software MRICron.

Results

Demographic information on frontal lobe damaged groups and matched healthy controls can be found in Table 1. These groups did not differ significantly in age, years of education or estimated IQ (One way ANOVAs: $F_s = 1.3$, $P_s = 0.3$), though there was an effect of group status on BDI-II scores ($F_{2, 42} = 4.25$, $P = 0.02$), with slightly higher scores in both the VMF and FC groups compared to healthy controls (between-subjects t-tests: $t_s = 4.05$, $P = 0.01$, uncorrected). Mean BDI-II scores were well below threshold for risk of clinical depression in all groups. There was also no significant difference between frontal lobe damaged groups in lesion volume (Mann-Whitney U test: $Z = 0.27$, $P = 0.8$). Performance in neuropsychological screening tests did not differ between frontal lobe damaged groups (between-subjects t-tests: $t_s = 1.70$, $P = 0.1$). Results from these screening tests can be found in Table 2.

Emotion detection in free viewing

We first aimed to replicate past work demonstrating that VMF damage affects recognition of subtle emotional expressions (Heberlein et al., 2008; Jenkins et al., 2014; Tsuchida & Fellows, 2012). We tested for effects of group status on pD scores for subtle expressions in each target emotion (Figure 2a). There was no effect of group status on recognition of subtle fear ($F_{2, 60} = 1.02$, $P = 0.4$), though the pD scores of the VMF group were numerically worse than control groups. There was, however, a marginal significant effect of group status for subtle disgust ($F_{2, 60} = 3.29$, $P = 0.04$). Post-hoc tests showed a significant difference between the FC and VMF groups (Bonferroni corrected t-test: $P < 0.05$), and no other

significant differences. As in past studies, there was no effect of lesion damage on detection of subtle happiness ($F_{2, 60} = 0.01$, $P = 0.9$).

We also tested for effects of group status on detection of extreme (i.e. prototypical) facial emotions (Figure 2b). Most past work has found that VMF damage does not affect detection of these exaggerated expressions (Hornak et al., 1996; Wolf et al., 2014). In line with these past findings, we found no significant main effect of group status on detection of extreme fear ($F_{2, 60} = 0.64$, $P = 0.5$), disgust ($F_{2, 60} = 0.71$, $P = 0.5$), or happiness ($F_{2, 60} = 0.01$, $P = 0.9$).

Emotion discrimination in free viewing

By asking subjects to judge facial expressions for multiple emotions, our task design also let us test the selectivity of subjects' judgments about the emotional labels for each stimulus. To examine whether people with frontal lobe damage differed from controls in their ability to discriminate emotions, we tested the interaction between group status and emotional labels on pD scores for each category of subtle and extreme facial expressions. There were no significant interactions for subtle fear, disgust or happiness ($F_{s, 4, 120} = 1.27$, $P = 0.3$). There were trends toward significance for this interaction in extreme fear and disgust ($F_{s, 4, 120} = 1.83$, $P = 0.1$), but not happiness ($F_{s, 4, 120} = 0.82$, $P = 0.5$).

As in past work (Tsuchida & Fellows, 2012), we also calculated a specificity index by comparing the pD scores for the target emotions to the average pD scores for the other emotions in each block. There was no significant effect of group status on this specificity index averaged across subtle expressions ($F_{2, 60} = 1.75$, $P = 0.2$), nor were there any significant effects of group status for any of the individual subtle emotional expressions (Figure 3a; $F_{s, 2, 60} = 1.90$, $P = 0.2$). In contrast, there was a significant effect of group status on the specificity of ratings for extreme emotional expressions ($F_{2, 60} = 3.86$, $P = 0.03$). Post-hoc tests revealed that the specificity indices for the VMF group were significantly lower than healthy controls for extreme expressions (Bonferroni corrected t-test: $P < 0.05$), but found no other significant differences. Analysis of separate extreme emotions found significant effects of group status on specificity indices for extreme fear ($F_{2, 60} = 3.12$, $P = 0.05$), and disgust (Figure 3b; $F_{2, 60} = 3.56$, $P = 0.03$). Post-hoc tests between groups for specificity scores in these two extreme emotions were not significant. However, the VMF and FC groups had numerically lower specificity scores than healthy controls for extreme fear, and the VMF group also had lower scores for extreme disgust than both control groups at an uncorrected threshold. There was no equivalent effect of group status on the specificity of ratings for extreme happy faces ($F_{2, 60} = 1.33$, $P = 0.3$).

Fixations during free viewing

We compared the total number of fixations subjects made to face stimuli to gauge any group differences in overall exploration of faces, independent of the distribution of fixation locations. We focused this analysis on neutral faces and subtle and extreme expressions that matched the target emotion for a given block, to measure how the strength of an expression affected exploration. Across groups, there was a significant main effect of emotional degree (Mixed measures ANOVA: $F_{2, 120} = 27.07$, $P < 0.0001$), with more fixations to subtle and

extreme emotional faces compared to neutral faces. There was also a significant three-way interaction between group status, degree and emotional target ($F_{8, 240} = 2.74, P = 0.007$). Full post-hoc tests did not reveal any significant differences between groups at a stringent Bonferroni correction threshold ($\alpha = 0.00185$). However, at an uncorrected threshold, the number of fixations to extreme disgusted faces was higher in the VMF group ($P = 0.04$), and FC group ($P = 0.01$), relative to healthy controls. There were no significant differences, even at an uncorrected threshold, between VMF and FC group total fixations across conditions. Importantly, there was no significant main effect of group ($F_{2, 60} = 1.10, P = 0.3$), nor any main effect for emotion target ($F_{2, 120} = 2.49, P = 0.08$). Thus, there was some trend for frontal lobe damaged groups to make more fixations while exploring extreme disgusted faces, but no other major differences between groups in their overall fixation rates during free viewing.

Next, we compared the distribution of fixations to facial features during free viewing of faces (Figure 4). Collapsing across task conditions, we found no significant effect of group status on the ILR transformed distribution of fixations across AOIs (multivariate ANOVA: Wilks' Λ : 0.96, $F_{4, 58} = 0.50, P = 0.3$). We also carried out univariate comparisons to test if raw fixation frequencies to individual facial features differed with group status. Across groups, the vast majority of fixations were made to the eyes, nose and mouth in the free viewing condition ($M = 98.6\%, SD = 2.6\%$), and so we focused on those features. Collapsing across all conditions during free viewing, there were no univariate main effects of group status on the proportion of fixations to the eyes (One-way ANOVA: $F_{2, 60} = 0.77, P = 0.5$), nose ($F_{2, 60} = 1.38, P = 0.3$), or mouth ($F_{2, 60} = 0.63, P = 0.5$).

We next tested if there were group differences in fixation allocation to different emotional expressions, when these expressions matched the block target emotion. As before, multivariate analyses of the frequency of fixations across facial features revealed no significant differences between groups for subtle fear, disgust or happiness (Wilks' Λ 's 0.83, F 's $_{4, 58} = 1.37, P$'s $= 0.2$). Separate univariate analyses on the frequency of fixations to the eyes, nose and mouth for each emotional expression revealed no significant differences between groups (One-way ANOVAs: F 's $_{2, 60} = 1.17, P$'s $= 0.3$), though a trend was found for fixations to the nose while viewing subtle happiness (F 's $_{2, 60} = 2.43, P = 0.09$), driven by a numerically lower frequency of nose fixations in the FC group, relative to the healthy control and VMF groups. We also found no differences between groups in the distribution of fixations to facial features for any extreme emotional expressions, either when compared using multivariate analyses (Wilks' Λ 's 0.92, F 's $_{4, 58} = 1.19, P$'s $= 0.3$), or more standard univariate comparisons (One-way ANOVAs: F 's $_{2, 60} = 2.30, P$'s $= 0.1$). There were also no effects of group status on the proportion of time subjects spent fixating facial features during free viewing (Supplementary Results).

Heat map comparison during free-viewing

In addition to the AOI comparisons described above, we tested if there were any finer grained differences in subjects' fixations during free-viewing of emotional expressions by directly comparing heat maps of subjects' fixations during the free viewing condition, collapsed across task conditions. Heat maps for each group were directly compared at each

pixel using t-tests, and a threshold for statistical significance was determined through permutation testing. There were no significant differences between the healthy control group and either frontal lobe damaged group that met the permutation threshold for statistical significance.

Fixation pattern during free viewing

The above results indicate that the overall distribution of fixations did not differ systematically between the VMF damaged group and control groups. However, it is possible that VMF damage caused more nuanced changes in the exploration of face stimuli, only evident during the early period of stimulus processing. Indeed, Wolf et al. (2014) found that VMF damaged subjects showed the most prominent reduction in fixations to the eye region early during face exploration. To test if this was the case here, we analyzed the first four fixations subjects made to face stimuli to determine if the fixation patterns of VMF damaged subjects differed substantially from control groups in these first few eye-movements. As can be seen in Figure 5, all groups typically first fixated the center of the face (the nose and cheeks), and there were no group differences in this pattern (Multivariate ANOVA: Wilks' $\lambda = 0.97$, $F's_{4, 58} = 0.44$, $P = 0.7$). While the VMF group looked to the eyes numerically less often in the second fixation compared to control groups, there was no statistical effect of group status (Wilks' $\lambda = 0.93$, $F's_{4, 58} = 1.04$, $P = 0.4$). This pattern held for the third and fourth fixations as well (Wilks' $\lambda = 0.88$, $F's_{4, 58} = 1.92$, $P's = 0.1$). Univariate comparisons of the raw fixation frequencies to the eyes, nose and mouth similarly did not find any differences between groups in the first four fixations (One-way ANOVAs: $F's_{2, 60} = 2.39$, $P = 0.1$).

We also analyzed the pattern of fixations using a similar method to Wolf et al. (2014), where broke down each trial into two epochs, each with a duration of one second. We found no effects of group status on the proportion of fixations to facial features in either epoch (Supplementary Results).

Relationship between free fixations and ratings

Although subjects with VMF damage showed normal fixation patterns during free viewing, they were moderately impaired in recognizing subtle disgust and differentiating extreme emotional expressions. These results contrast with findings in neuropsychiatric populations where impairments in facial emotion recognition often accompany unusual fixation patterns. To test if there was any overall relationship between behavioral performance and fixations to different face AOIs, we carried out multiple linear regression analyses between pD and specificity indices and the ILR transformed frequency of fixations to the eyes, nose and mouth. There was a trend toward a relationship between the pattern of fixations and pD scores for subtle happiness ($F_{3, 59} = 2.68$, $P = 0.06$), which was driven by an inverse relationship between pD scores and the frequency of fixations to the nose (OR = 0.51, 95% CI: 0.30–0.89, $P = 0.01$). However, there were no significant associations between the frequency of fixations to facial features and pD scores for any other subtle emotional expressions ($P's = 0.2$). There were no significant relationships between fixations to facial features and recognition of any extreme emotional expressions ($P's = 0.09$).

Specificity indices were also not significantly related to fixation patterns for any subtle emotional expression ($F_{3, 59} = 1.34$, $P = 0.3$). There was a trend toward a significant association for the specificity of extreme disgust ratings ($F_{3, 59} = 2.61$, $P = 0.06$), driven by an inverse relationship between fixations to the nose and specificity (OR = 0.52, 95% CI: 0.32–0.86, $P = 0.008$), but no significant relationships with eye or mouth fixations. The associations of specificity indices and fixations for extreme fear and happiness were also non-significant ($F_{3, 59} = 1.88$, $P = 0.1$).

Voxel-based lesion symptom mapping

The behavioral results during free-viewing contrast with those of Wolf et al. (2014), who found that damage to VMF reduced fixations to the eyes. One potential explanation for these discrepancies is the anatomical resolution of this region-of-interest approach: i.e. if effects are localized to a smaller sub-region within VMF affected in only a subset of the patients assigned to this group, this signal might not be detected in overall group performance. To examine the effects of lesion damage at a finer resolution, we used voxel-based lesion symptom mapping (VLSM), a method that carries out voxel-wise tests for the association of a deficit with the lesion damage (Bates et al, 2003). We tested where damage was associated with impaired emotion recognition and reduced frequency of fixations to the eyes during free-viewing, collapsed across conditions (Supplementary Results). There were no voxels associated with decreased average pD scores, nor the reduced frequency of fixations to the eyes, that passed the permutation corrected threshold for statistical significance.

Emotion detection in gaze-contingent viewing

We next asked subjects to judge faces for fear, while viewing face stimuli through a gaze-contingent window. This manipulation places demands on top-down control to selectively direct eye-movements to the location of facial features that are informative about the emotional expression in the absence of a stimulus. Previous work has demonstrated that bilateral amygdala damage decreases fixations to the eyes of face stimuli during free viewing, but not when faces are viewed through a gaze-contingent aperture (Kennedy & Adolphs, 2010), suggesting that bottom-up and top-down control over fixations to face stimuli are under the control of different neural processes. Here, we tested if directed control of fixations to face stimuli is affected following VMF damage.

There was no significant effect of group status on pD scores for subtle fear (Figure 6; One-way ANOVA: $F_{2, 60} = 2.17$, $P = 0.1$), though both the FC and VMF groups had numerically lower average pD scores compared to healthy controls. Similar results were found for detection of extreme fear ($F_{2, 60} = 1.95$, $P = 0.1$).

Emotion discrimination in gaze-contingent viewing

We also tested the interaction of group status and emotional labels to test for group differences in the specificity of fear ratings during gaze-contingent viewing. This interaction was significant for subtle (Mixed-measures ANOVA: $F_{4, 120} = 2.81$, $P = 0.03$), but not extreme fear ($F_{4, 120} = 1.05$, $P = 0.4$). Post-hoc tests between groups for subtle fear ratings were not significant after correction for multiple comparisons, but indicated that the FC group tended to rate happy faces as more afraid compared to healthy controls. We also

calculated a specificity index for subjects' ratings in the gaze-contingent condition. There were no effects of group status on this measure for subtle or extreme emotional expressions (One-way ANOVAs: $F_{2,60} = 2.19$, $P = 0.1$).

Fixations during gaze-contingent viewing

We examined group differences in the number of fixations during gaze-contingent viewing, and if there were specifically any differences between groups when viewing neutral faces, or subtle and extreme fear. There were no main effects of group status or emotional degree, however there was a trend for the VMF group to make fewer fixations to neutral faces compared to the FC and healthy control groups (Supplementary results).

As in the free-viewing condition, we compared the distribution of fixations during gaze-contingent viewing using both multivariate and univariate approaches (Figure 7). No effect of group status was found on the distribution of fixations to facial features during gaze-contingent viewing, averaged across task conditions (multivariate ANOVA: Wilks' $\Lambda = 0.93$, $F_{4,58} = 1.01$, $P = 0.4$). We also compared fixations to faces displaying fear specifically, as this was the target emotion in the block. There was a significant effect of group status in fixations to extreme afraid faces (Wilks' $\Lambda = 0.83$, $F_{4,58} = 2.87$, $P = 0.03$), but not subtle afraid faces (Wilks' $\Lambda = 0.92$, $F_{4,58} = 1.15$, $P = 0.3$). To test the source of group differences for extreme afraid faces, we carried out one-way ANOVAs on the ILR transformed fixation frequency to each feature. These tests found significant differences between groups for fixations to the eyes ($F_{2,60} = 6.06$, $P = 0.004$), nose ($F_{2,60} = 4.94$, $P = 0.01$), and chin ($F_{2,60} = 3.95$, $P = 0.02$). Post-hoc t-tests revealed that the FC group looked to the eyes of extreme afraid faces less than healthy controls (Bonferroni corrected t-test: $P < 0.01$), and looked to the nose and chin more often (Bonferroni corrected t-tests: $P < 0.05$). There were no significant differences between the VMF group and either control group. A similar pattern of results was found in univariate contrasts of the raw frequency of fixations and dwell time spend on AOIs (Supplementary Results).

Heat map analysis in gaze-contingent viewing

Heat maps for fixations collapsed across conditions during free-viewing were directly compared between groups using massive univariate tests. There were no differences that survived correction for multiple comparisons based on the permutation derived threshold for statistical significance.

Fixation pattern during gaze-contingent viewing

For a more granular analysis of fixation patterns in gaze-contingent viewing, we tested if there were group differences in the distribution of the first four fixations to facial features, collapsed across all task conditions (Figure 8). Multivariate ANOVAs for the first four fixations did not show any significant effects of group status (Wilks' $\Lambda = 0.91$, $F_{4,58} = 1.37$, $P = 0.3$). We also carried out univariate comparisons for fixation frequencies to the eyes, nose and mouth. Here we found a significant effect of group status on the frequency of nose fixations for the first fixation ($F_{2,60} = 3.98$, $P = 0.02$). Post-hoc tests revealed this was due to the increased frequency of nose fixations in the FC group compared to health controls (Bonferroni corrected t-test: $P < 0.05$). While the VMF damaged group looked to the eyes

numerically less than both control groups in the second, third and fourth fixations, there were no significant effects of group status for fixation frequency to any facial features in these conditions ($F_{s\ 2, 60} = 2.49, P = 0.09$).

We also analyzed fixation patterns by testing the proportion of fixations to features in one-second epochs during the viewing period, like in Wolf et al. (2014). We found no effect of group status on the proportion of fixations to facial features in either the first or second epoch using this approach (Supplementary Results).

Relationship between gaze-contingent fixations and ratings

We tested for a relationship between fear pD scores and fixations to different face regions to examine how fixating facial features affected performance when subjects' view was restricted to the gaze-contingent aperture. We carried out multiple linear regression between pD scores and specificity indices for subtle and extreme afraid faces with the ILR transformed frequency of fixations to the eyes, nose and mouth. There was a significant relationship between pD scores for extreme fear and fixations ($F_{3, 59} = 5.52, P = 0.002$), driven by a positive relationship between fixations to the eyes and pD scores (OR = 1.70, 95% CI: 1.09–2.66, $P = 0.01$), and no significant effects for the nose (OR = 0.92, 95% CI: 0.60–1.43, $P = 0.7$), or mouth (OR = 0.66, 95% CI: 0.41–1.06, $P = 0.07$). There was also a significant, but weaker, relationship between fixations and subtle fear pD scores ($F_{s\ 3, 59} = 2.76, P = 0.05$), driven by a significant inverse relationship between nose fixations and pD scores for subtle fear (OR = 0.64, 95% CI: 0.43–1.00, $P = 0.03$), but no significant relationship between fixations to the eyes (OR = 1.15, 95% CI: 0.77–1.72, $P = 0.5$), or mouth (OR = 0.83, 95% CI: 0.52–1.33, $P = 0.4$). There were no comparable significant relationships between fixations and the specificity index for subtle or extreme fear in the gaze-contingent condition ($F_{s\ 3, 59} = 0.85, P = 0.5$).

Emotion detection during instructed viewing

Previous work has shown that experimentally manipulating the location of gaze can affect emotion recognition performance (Peterson & Eckstein, 2012). In particular, directing fixations to the eye region has been shown to improve fear recognition performance in a patient with bilateral amygdala damage (Adolphs et al., 2005). We tested if participants would benefit from such instructions here.

Despite explicit instructions to fixate only the eyes, six frontal lobe damaged subjects made fixations to other parts of the face. Given that the manipulation had failed in these individuals, we removed them from further analysis (see Methods). In the remaining subjects, we first tested for any change in pD scores for subtle afraid faces between directed viewing of the eyes and free viewing. Collapsing across groups, there was a significant increase in pD scores for subtle afraid faces when subjects were instructed to look at the eyes, compared to free viewing (One sample t-test: $t(56) = 2.13, P = 0.04$), but not for extreme fear ($t(56) = 1.02, P = 0.3$). Thus, directing gaze to the eye region improved detection of subtle, but not extreme, fear. These data support previous work that has suggested that information from this region is especially useful in detecting fear (Smith et al., 2005), particularly for subtle expressions (Vaidya et al., 2014).

Although the VMF group had numerically lower pD scores for afraid faces than those of the FC and healthy control group during directed fixation of the eyes, there was no significant effect of group status on pD scores for subtle afraid emotional faces (Figure 9a; One-way ANOVA: $F_{2, 60} = 1.39$, $P = 0.3$). We also compared the change in subtle fear pD scores between free viewing and instructed fixation to the eyes to test if VMF damage affected the change in performance between these conditions, if not overall pD scores. Again, we found no significant effect of group status (Figure 9b; $F_{2, 60} = 0.78$, $P = 0.5$). Null results were also found for the same analyses on pD scores for extreme afraid expressions (Figure 9c–d; $F_{2, 60} = 0.59$, $P = 0.6$).

Emotion discrimination during instructed viewing

As in free and gaze-contingent viewing, we tested if there were group differences in the specificity of fear ratings when subjects were instructed to only look at the eyes. The interaction of group status and emotional expression was not significant for subtle or extreme stimuli (Mixed measures ANOVA: $F_{4, 120} = 2.08$, $P = 0.09$). We also compared groups on a specificity index corrected for pD scores related to detection of the target emotion. There was a trend toward significance for extreme emotions (One-way ANOVA: $F_{2, 60} = 2.90$, $P = 0.06$), and a significant effect for subtle emotions ($F_{2, 60} = 3.93$, $P = 0.02$). Post-hoc tests showed that the specificity index for subtle fear was significantly lower for the FC group compared to healthy controls (Bonferroni corrected t-test: $P < 0.05$), but no other significant differences.

Discussion

Here, we examined the necessary contributions of VMF to detecting, discriminating and examining emotional facial expressions. VMF damage had a modest effect on the recognition of subtle disgust during free viewing, partially replicating past work from our group (Heberlein et al., 2008; Tsuchida & Fellows, 2012), and others (Jenkins et al., 2014). Participants with VMF damage also demonstrated greater confusion between extreme emotional categories, particularly when judging faces for disgust. However, analysis of subjects' fixations during free viewing did not reveal any reduced tendency to fixate the eyes in patients with VMF damage. Similarly, there were no differences in eye movements during gaze-contingent viewing, and instruction to fixate the eye region did not change the performance of VMF damaged subjects. These results argue that VMF damage may affect the interpretation of emotional content in faces, without affecting the pattern of fixations to facial expressions.

Our data in the free viewing condition are inconsistent with a recent study by Wolf et al. (2014), which found that three subjects with bilateral VMF lesions looked to the eye region less when examining emotional faces. In the current study, we were able to test for this behavior in a larger sample of subjects with VMF damage, including three subjects with bilateral damage very similar to the subjects studied by Wolf et al. (2014). While we found a modest tendency for VMF damaged subjects to fixate the eye region less across conditions, this difference was not significant in any particular condition, and was not evident in patients with bilateral VMF damage. The increased power of the current study gives us confidence in

arguing that VMF damage does not cause significant changes in fixation patterns to face stimuli. The stimuli and general design of the current study and Wolf et al. (2014) were quite similar. One notable difference is that subjects in the current study were required to fixate a peripheral cross that did not overlap with the face stimulus before each trial. In contrast, face stimuli replaced a central fixation cross in Wolf et al. Without any need to saccade to the face stimulus, subjects likely felt less need to move their fixation away from the center of the face. However, in the current study, subjects had to saccade to the face to see features in detail. We made this design choice to reduce the bias of subjects' starting fixations and encourage subjects to actively seek visual information. This small difference might explain the failure to replicate the observations in Wolf et al. If the "default" starting position is crucial to effects, it raises general questions about the ecological validity of such experiments. Real world emotion recognition likely most often involves directing gaze from elsewhere to the key regions of the face, in a given context, rather than beginning at the center of the face and then seeking information from other facial features.

The current study partially replicates behavioral findings from past work from our group and others, while also providing some new results. Past work has found that VMF damage causes reduced sensitivity to a range of subtle emotions (Heberlein et al., 2008; Jenkins et al., 2014; Tsuchida & Fellows, 2012). Here, these deficits were not found for fear recognition. One possible reason for this inconsistency is the greater difficulty of the current task: the Cohen's d for controls' average ratings of subtle emotional targets against neutral expressions in Tsuchida and Fellows (2012) was 3.98, while in the current study it was 3.08. Greater variance in control performance may have reduced our ability to detect deficits in the lesion groups. This study also differs in some substantial ways from past work from our group: here we used a different stimulus set that included extreme emotions, and asked subjects to judge fewer target emotions and emotional expressions. These differences may have influenced the strategies adopted by both healthy controls and frontal lobe damaged subjects. For example, the presence of extreme expressions may have caused healthy subjects to adopt a higher threshold for emotion recognition, reducing sensitivity to subtle expressions.

Critically, our findings indicate that VMF-associated impairments in emotion recognition are unlikely to be due to a failure to search for emotionally informative features. Fixation patterns of those with VMF damage in the gaze-contingent condition were very similar to the patterns of healthy controls, indicating a preserved ability to deliberately search out informative features. Instructing subjects to fixate the eye region also did not yield a greater improvement in fear recognition in the VMF group compared to controls, arguing that these subjects did not glean any additional information from the eyes above and beyond healthy controls. We chose to focus exclusively on the fear condition in these two fixation manipulations, given the existing evidence indicates that visual information from the eyes is important for recognizing this emotion (Adolphs et al., 2005; Smith et al., 2005), and a pragmatic concern about the length of the testing session. We did not find the expected impairment in detecting fear in the VMF group during free viewing, limiting our ability to detect improvements in performance during instructed viewing. However, VMF damaged subjects were consistently numerically worse than healthy controls in judging subtle fear in all experimental conditions and did not show any difference in the pattern of their fixations

across conditions. Together, these data argue that deficits in emotion recognition related to VMF damage are unlikely to be caused by a failure to fixate relevant, informative facial features.

As in Tsuchida and Fellows (2012), there was no deficit in the specificity of ratings for subtle expressions in the VMF group. However, while participants with VMF damage could detect extreme emotional expressions, we found that they were less specific in their ratings of these faces. This is a novel result that was not predicted from past studies. Combined with the relatively modest impairments in detecting emotional expressions, these data suggest that subjects with VMF damage may have used a lower threshold for emotion detection strategically, at the expense of reduced specificity.

These findings complement the extensive work characterizing the deficits of SM, a patient with selective bilateral amygdala lesions. SM showed reduced fixations to the eyes during free viewing and naturalistic conversations, but looked to this area in gaze-contingent viewing, and showed an improvement in fear recognition when instructed to look at the eyes (Adolphs et al., 2005; Kennedy & Adolphs, 2010; Spezio, Huang, Castelli, & Adolphs, 2007). Thus, unlike VMF damage, deficits in fear recognition after amygdala lesions appear to be due to disruption of a bottom-up biasing of gaze towards informative facial features during more naturalistic viewing, which can be corrected by instruction or need for a top-down strategy in searching facial expressions. We suggest that the VMF plays a role in emotion recognition distinct from the role of the amygdala. VMF seems to be necessary for the interpretation of emotional information in a broad array of emotional categories, rather than in orienting attention to features where this information is visually available. How VMF is implicated in the interpretation of emotional faces is not clear. Increased noise in the representations of facial emotions could explain both deficits in detecting subtle emotions, and reduced specificity in rating extreme emotions, if this noise grows parametrically with emotional signals. Alternatively, VMF damage might hinder the ability of subjects to focus on multiple relevant dimensions of emotional stimuli like arousal and valence (Russell, 1980). For example, these subjects might focus heavily on arousal when judging extreme emotions while blurring distinctions between emotional categories.

Unlike the VMF group, the FC group appeared to struggle more in the gaze-contingent condition, making more fixations to the nose region than healthy controls and providing less specific ratings for subtle fear. This result is consistent with a role for prefrontal regions outside of VMF in goal-directed, top-down control of eye movements and attention (Desimone & Duncan, 1995; Guitton, Buchtel, & Douglas, 1985). The FC group also had lower specificity for subtle fear in the instructed viewing condition. Frontal lobe damage outside VMF thus appeared to affect the specificity of fear judgments based on limited visual information (such as only the eyes). We previously found that left lateral frontal damage reduced the specificity of judgments about subtle emotional expressions (Tsuchida & Fellows, 2012), however the lesion distribution in the current study provided less power to detect effects of damage to this region.

The relationship between fixations and behavior also was weaker in the current study than expected. In a previous study in healthy young people using the same stimuli, we found

more robust relationships between pD scores and fixations during free viewing for subtle emotions (Vaidya et al., 2014). In that study, faces subtended $17.2 \times 22.4^\circ$ of visual angle, while in this study faces covered $10.7 \times 15.0^\circ$. This increased the amount of visual information available immediately outside of the fixated region, potentially weakening relationships between fixation location and recognition. However, the dimensions of stimuli in the current study are similar to those used in other studies of fixations and emotion recognition in healthy individuals (approximately $12\text{--}15^\circ$ of vertical visual angle (Jack, Blais, Scheepers, Schyns, & Caldara, 2009; Peterson & Eckstein, 2012; Schurgin et al., 2014), and larger than those used in Wolf et al. (2014) (11.5°). The relationship between fixations and behavior was also much stronger in the gaze-contingent condition, where extra-foveal information was not available. Instruction to look at the eyes improved detection of subtle fear, consistent with the hypothesis that this region is especially informative about this emotion (Adolphs et al., 2005; Peterson & Eckstein, 2012; Smith et al., 2005). Together, these results indicate that demands on fixation behavior may be manipulated either by changing the dimensions of the face in visual angle, or by obscuring features outside the fovea, as in the gaze-contingent condition. Future work may take advantage of these manipulations to increase sensitivity to detect gaze-dependent deficits in emotion recognition in other populations.

This research has broader relevance to a growing literature examining the neurobiological circuitry involved in social behavior. While VMF is frequently activated in social and emotional tasks (Roy, Shohamy, & Wager, 2012), the contributions of this region to these processes are unclear. Lesion studies have found that VMF damage disturbs social behavior in real-life, and the ability to generate solutions to social problems in the laboratory (Barrash, Tranel, & Anderson, 2000; Peters, Fellows, & Sheldon, 2017), and impairs theory of mind (Shamay-Tsoory, Aharon-Peretz, & Perry, 2009; Stone, Baron-Cohen, & Knight, 1998). Our results argue that these social deficits do not stem from a failure to perceptually attend to socially relevant information, but an inability to interpret these signals. These findings are relevant to neuropsychiatric disorders marked by impairments in social awareness and emotion recognition. For example, autistic children with deficits in social cognition do not necessarily differ from typically developing counterparts in their fixation patterns to face stimuli (Guillon, Hadjikhani, Baduel, & Roge, 2014), suggesting that these impairments might arise (at least in some cases) from misunderstanding social signals, rather than a failure to attend to them. Our data indicate that VMF may play a critical role in more nuanced aspects of interpreting social cues, rather than controlling the processes by which this information is sampled. This work thus furthers the goal of understanding the neurobiological mechanisms underlying social behavior in healthy individuals and contributes causal evidence to a neurobiological framework for understanding disordered social behaviors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Representative axial slices and sagittal view of overlap of lesion tracings registered to the MNI brain. Rows show overlap in the frontal control (FC) and ventromedial frontal (VMF) groups, as well as bilateral-VMF damaged subjects. Numbers above slices indicate z-coordinates of axial section in MNI space. Left sagittal view shows the left hemisphere, right view shows the right hemisphere. Colors indicate number of subjects with overlapping lesions, as indicated by the color bar. L, Left; R, right.

Figure 2.

Proportional difference (pD) scores for emotion ratings in the free-viewing condition. **a.** Subtle emotional expressions, **b.** Extreme emotional expressions. Each dot represents a subject from the healthy control (CTL), frontal control (FC) or ventromedial frontal (VMF) groups. x-axis labels correspond to the emotion of the stimulus, while panel labels correspond to the target emotion for the block. *, $P < 0.05$, Bonferroni corrected t-test. Crosses indicate mean (horizontal) and SEM (vertical) for each group.

Figure 3.

Residuals from specificity index of emotion ratings during free-viewing, corrected for pD scores. **a.** Subtle emotional expressions, **b.** Extreme emotional expressions. *, $P < 0.05$, one-way ANOVA for effects of group status. Crosses indicate the mean (horizontal) and SEM (vertical) for each group.

Figure 4. Heat maps and proportion of total fixations to areas of interest during free viewing collapsed across all conditions. Orange dots in VMF group represent subjects with bilateral VMF damage. Crosses indicate mean (horizontal) and SEM (vertical).

Figure 5. Mean proportion of fixations to facial features during first four fixations of free viewing. Each line represents a single subject. Black dashed lines with orange markers indicate subjects with bilateral VMF damage.

Figure 6. Proportional difference scores for subtle and extreme emotional expressions in the gaze-contingent viewing condition. Crosses indicate group means (horizontal line) and SEM (vertical lines).

Figure 7.

Heat maps and proportion of total fixations to areas of interest during gaze-contingent viewing collapsed across all conditions. Orange dots in VMF group represent subjects with bilateral VMF damage. Crosses indicate mean (horizontal) and SEM (vertical).

Figure 8. Mean proportion of fixations to facial features during first four fixations of gaze-contingent viewing. Each line represents a single subject. Black dashed lines with orange markers indicate subjects with bilateral VMF damage.

Figure 9.

Behavioral performance when instructed to view the eyes. **a, c.** Proportional difference (pD) scores for subtle and extreme emotional expressions in the instructed viewing condition. Crosses indicate group means (horizontal line) and SEM (vertical lines). **b, d.** Change in pD scores between instructed viewing and free-viewing conditions for subtle and extreme fear.

Table 1.

Demographic information for healthy matched controls (CTL), frontal lobe damaged controls (FC), and ventromedial frontal lobe damaged subjects (VMF). Values represent means with standard deviations in parentheses, except for lesion volume where the median and range are provided.

Group	Age (years)	Sex (M/F)	Education (years)	BDI-II	AMNART IQ ^a	Lesion Volume (cc)
CTL (N=26)	58.0 (11.5)	7/19	16.3 (3.1)	4.0 (4.7)	121 (5)	-
FC (N = 20)	55.4 (9.6)	7/13	15.0 (3.7)	9.1 (6.8) *	118 (6)	23 (3–96)
VMF (N = 17)	59.5 (11.4)	5/8	15.6 (2.9)	8.1 (5.2) *	119 (6)	16 (7–77)

^aNot all subjects were able to complete the AMNART.

* $P < 0.05$, two-tailed t -test against control scores, uncorrected

Table 2.

Performance on neuropsychological screening tests for frontal lobe damaged controls (FC) and ventromedial frontal lobe damaged subjects (VMF). Values represent means with standard deviations in parentheses.

Group	Incidental memory P(Correct)	Fluency -animals	Fluency - F	Backwards Digit Span	Sentence comprehension P(Correct)
FC ^a	0.78 (0.14)	19.8 (7.9)	11.3 (5.1)	2.7 (1.1)	0.97 (0.06)
VMF ^a	0.86 (0.10)	19.8 (3.7)	10.8 (5.0)	3.1 (1.4)	0.98 (0.06) ^b

^aData missing from one subject

^bData missing from two subjects.