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Emotional reactivity following surgery to the prefrontal cortex

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Abstract

We aimed to elicit emotion in patients with surgically circumscribed lesions of the prefrontal cortex (PFC) in order to elucidate the precise functional roles in emotion processing of the discrete subregions comprising the ventromedial PFC, including the medial PFC and orbitofrontal cortex (OFC). Three components of emotional reactivity were measured: subjective experience, behaviour and physiological response. These included measures of self-reported emotion, observer-rated facial expression of emotion

and measurements of heart rate and heart rate variability during film viewing, and a measure of subjective emotional change since surgery. Patients with lesions to the ventromedial PFC demonstrated significant differences compared to controls in heart rate variability during the film clips, suggesting a shift to greater dominance of sympathetic input. In contrast, patients with lesions restricted to the OFC showed significant differences in heart rate variability suggesting reduced sympathetic input. They also showed less facial expression of emotion during positive film clips, and reported more subjective emotional change since surgery compared to controls. This human lesion study is important for refining theoretical models of emotion processing by the ventromedial prefrontal cortex, which until now have primarily been based on anatomical connectivity, animal lesion and human functional neuroimaging research. Such theories have implications for the treatment of a wide variety of emotional disorders.

Introduction

The ventromedial prefrontal cortex (VMPFC) is a brain area that has been found to be crucially involved in social and emotional functioning (Bechara, Damasio, & Damasio, 2000; Damasio & Anderson, 2003). Patients with damage to the bilateral VMPFC are often described as socially disinhibited, impulsive, sometimes complain of blunted affect, have poor judgment and decision-making, difficulty monitoring themselves, and lack awareness of their behaviour (Barrash et al., 2000; Beer et al., 2006; Eslinger and Damasio, 1985). This has resulted in patients with VMPFC lesions being likened to sociopaths (Blair and Cipolotti, 2000; Eslinger and Damasio, 1985).

Existing models of emotional dysfunction argue that the prefrontal cortex (PFC) may modulate emotional responses or related activity generated by subcortical areas (Phan, Wager, Taylor, & Liberzon, 2004; Quirk & Beer, 2006). For example, Mayberg (1997) presented a model of depression involving reciprocal inhibition, whereby depressed patients and healthy patients with induced sadness have increased activity in ventral paralimbic areas and decreased activity in the dorsal neocortex. Another prominent neurobiological model of emotion postulates that the VMPFC is important for emotion regulation via its inhibitory control of the amygdala. For example, Thayer and

Lane (2009) have described a *neurovisceral integration* model, which argues that the amygdala is vigilant for biologically relevant information, and that the PFC, including the orbitofrontal cortex (OFC) and medial PFC (MPFC), tonically inhibit the amygdala. This top-down inhibition is posited to modulate subcortical areas, which sculpt the subjective experience of emotion. The MPFC modulates amygdala activity both via projections to inhibitory interneurons (Rosenkranz & Grace, 2002), and via direct projections to areas important for emotional output, including autonomic, endocrine and motor regions (Öngür & Price, 2000). The OFC also modulates amygdala activity (Rempel-Clower, 2007) based on top-down evaluations of emotional significance calculated from current reward value (Rolls, 2004), and these functions are important for subjective emotional experience. This amygdala inhibition occurs via projections to inhibitory interneurons, and also via direct projections to emotional output areas (Rempel-Clower, 2007), albeit not as strong as those of the MPFC.

Whilst acknowledging that much evidence favours models of top-down inhibitory control of the amygdala by the VMPFC, in their review of data from primarily animal lesion and human neuroimaging studies, Myers-Schulz and Koenigs (2012) argued that models that argue that disorders of mood and emotion are simply a failure of the VMPFC to inhibit amygdala activity are not sufficient to adequately explain the complexities of emotional dysfunction. For example, although some evidence indicates that VMPFC inhibits stress-related sympathetic activity, including glucocorticoid secretion (Urry et al., 2006), cardiac changes (Wager et al., 2009), and electrodermal responses (Milad et al., 2007), studies in animals (Jahn et al., 2010; Radley, Arias, & Sawchenko, 2006) and patients with VMPFC lesions (Damasio, Tranel, & Damasio, 1990) have found evidence to the contrary. To account for these incongruent findings, Myers-Schulz and Koenigs (2012) argued that there is a functional differentiation within subregions of the VMPFC, and emphasised "the need for a more fine-grained model that can better account for the vmPFC's seeming disparate roles in affective states" (p. 2). In line with this, the present study aimed to determine the functional differentiation of the subcomponents of the VMPFC in emotion.

The VMPFC is a heterogenous region comprised of several distinct cytoarchitectonic areas (Roy, Shohamy, & Wager, 2012) that also differ in anatomical

connectivity. Thus, the orbital and medial portions of the VMPFC may be expected to play overlapping but different roles in emotion for both positive and negative emotional states (Myers-Schulz & Koenigs, 2012). While some attempt has been made to determine the precise neuroanatomical subregions of the PFC that are involved in emotion perception (Hornak et al., 2003) as well as social cognition ([redacted] et al., 2014), no study has empirically tested the relationship between specific lesion location and emotional reactivity, which involves the three domains of subjective feeling, behavioural expression, and physiological emotional response.

The present study is the first to our knowledge that aimed to elicit emotion in an experimental setting in patients following discrete, circumscribed surgical lesions of the prefrontal cortex. This was achieved using an emotion elicitation paradigm using film stimuli and measuring all three components of the emotional response. As per previous research (Hornak et al., 2003), we included as a control group patients with lesions to the dorsolateral PFC (DLPFC), as this region is not involved in emotional reactivity. As an additional control group, we measured a group of patients who had undergone non-cerebral neurosurgery. Because the DLPFC is not directly involved in emotion, we hypothesised that this group would not differ significantly on any measures to the control group. Based on findings of blunted affect (Eslinger and Damasio, 1985; Barrash, Tranel and Anderson, 2000), reduced somatic responses (Damasio, Tranel, & Damasio, 1990), and impaired facial emotion perception and theory of mind ([redacted] et al., 2014) following lesions to the VMPFC in humans, we hypothesised that compared to a HC group, patients with VMPFC lesions would demonstrate reduced subjective experience of emotion in response to film clips, reduced cardiac reactivity, reduced facial expression of emotion, and greater subjective emotional changes since surgery. With the lack of human lesion research investigating the role of VMPFC subregions in emotional reactivity, and the limitations in cross-species comparisons of VMPFC regions (Myers-Schulz and Koenigs, 2012), it was difficult to make confident hypotheses regarding the OFC and MPFC groups, thus our hypotheses relating to these two groups were more exploratory, although we expected similar findings to the VMPFC group, however not as severe, given that the lesions were restricted to only one region and not both (as in the VMPFC group).

Method

Participants

This sample has been described in a previous paper that examined social cognition ([redacted] et al., 2014). Participants were 27 patients who had undergone neurosurgery to the PFC, with a single surgical resection cavity. Reasons for surgery were: primary brain tumour (*n*=21), single metastatic tumour (*n*=2), angioma (*n*=1), epidermoid cyst (*n*=1), abscess (*n*=1) and bone fragment (*n*=1). Control participants were 26 patients who had undergone spinal surgery (cervical or lumbar laminectomy, discectomy or rhizolysis). Participants were aged over 18 years and tested within 1-12 months post-operative to reduce the potential influence of compensatory recovery mechanisms. Consent was obtained and all procedures were conducted according to the declaration of Helsinki (Br Med J 1964; 2: 177-178) and approved by the Human Research Ethics Committees of [redacted], The Royal Melbourne Hospital and St Vincent's Hospital, Melbourne, Australia. Exclusion criteria were nerve sheath tumour, neurological disease other than reason for surgery, heart disease, documented cerebral trauma, vision or hearing problems other than corrective lenses, and poor English comprehension and expression [score <13 on the Frenchay Aphasia Screening Test (Enderby, Wood, Wade, & Langton Hewer, 1987)].

MRI analysis

Lesion site and volume was ascertained from post-surgical structural MRI scans closest to the date of testing. The brain regions were segmented from these images using the Brain Extraction Tool (BET; Jenkinson, Pechaud, & Smith, 2005; Smith, 2002) within the brain image analysis package FSL 4.1 (Smith et al., 2004; Woolrich et al., 2009). These brain extracted images were then normalised by co-registration to the Montreal Neurological Institute (MNI) 2mm standard brain using a 12 parameter affine algorithm (FLIRT; Jenkinson, Bannister, Brady, & Smith, 2002; Jenkinson & Smith, 2001) within FSL. 'Analyze' software (version 9.0 Mayo Clinic, Biomedical Imaging Resource) was used to manually correct for inaccuracies in automatic segmentation and

to segment the lesions by outlining regions of interest (ROIs) around the resection cavity on all image slices. All ROIs were traced by the primary author (LMJ) and confirmed by a neuroradiologist (PP).

Participants were assigned to the group for which they had the largest percentage of resection (see [redacted] et al., 2014 for details, including 3D ROIs online). Participants with more than five per cent resection of the ACC and more than five per cent resection of the OFC were assigned to a VM group. Patients with BA25 lesions also had orbital lesions, so were included in the VM group, therefore the ACC group comprised patients with pregenual and dorsal ACC lesions. The lesion locations of individuals in the brain surgery group are presented in Figure 1.

(Figure 1 here)

A Fisher's exact test found no significant difference in WHO tumour grade (Louis, Ohgaki, Wiestler, Cavenee, Burger, Jouvet, et al., 2007) between groups. There was however a significant difference between groups in lesion volume (Kruskal-Wallis test) $H(3)= 12.26$, $p= .007$ (ACC= 1234.50 ± 253.58 mm^3; Orbital= 881.14 ± 861.48 mm^3; VM= 5563.40 ± 4828.69 mm^3; DL= 914.45 ± 736.73 mm^3). The VM group had the largest lesions compared to all other groups. This was expected given the VM area is comprised of two areas. Point-biserial correlations between each group and lesion volume found a significant coefficient for the VM group, $r_{pb}= .624$ ($p< .001$), indicating that 38.93% of the variance in lesion volume was accounted for by VM location. Lesion volume therefore was a potential confounding factor. In order to determine whether group effects remained after controlling for lesion volume, a hierarchical regression (described below) was favoured over a covariate approach due to the sample size.

Group demographic characteristics

Table 1 presents demographic results. Participants were of a variety of nationalities, however Fisher's exact tests found no significant differences between groups in the proportion of participants who spoke English as a second language (ESL), proportion of males and females, age, days since surgery, or years of education.

(Table 1 about here)

Measures and apparatus

Screening instruments

Unilateral neglect was screened for with the *Benton Line Bisection Test* (Schenkenberg, Bradford, & Ajax, 1980). Aphasia was screened for with the *Frenchay Aphasia Screening Test: Comprehension and Expression subtests* [FAST*;* (Enderby et al., 1987)]. Sustained attention was measured with the *Test of Everyday Attention (TEA) Elevator Counting Subtest* (Robertson, Ward, Ridgeway, & Nimmo-Smith, 1994). Nonverbal IQ was estimated with the *Weschler Adult Intelligence Scale-III Picture Completion Subtest* [WAIS; (The Psychological Corporation, 1997)]. Full-scale IQ was estimated with the *Wide-Range Achievement Test 3- Reading Subtest* (WRAT-R), using an age-corrected standard score (Wilkinson, 1993). Handedness was measured with the *Edinburgh Handedness Inventory* (Oldfield, 1971).

No patient had unilateral neglect. There were no significant group differences for the FAST scales or the WAIS Picture completion score. However, an ANOVA found a significant effect of group for WRAT-R standard score, $F(4, 48) = 2.65$, $\eta_p^2 = 0.18$, $p = .045$. Post hoc tests found that the control group (M=103.77, SD=8.34) had significantly higher WRAT-R standard score than the ACC group (M=91.50, SD=9.47, $p = .012$) and the DL group (M=97.17, SD=11.63, $p = .015$). Furthermore, a Kruskal-Wallis test found that there was a significant difference between groups in TEA score, $H(4) = 34.20$, $p < .001$,with a ceiling effect observed for the orbital, DL and control groups. Follow-up Mann-Whitney tests found that the ACC (M=6.75, SD=0.50) and VM (M=6.20, SD=0.45) groups scored significantly lower than the control group (M=7.00, SD=0.00), with $p = .011$ and $p < .001$, respectively.

Film clips

Verbal and nonverbal standardised film clips elicited the target emotions of amusement, anger, disgust, fear, happiness and sadness ([redacted]). As

it was decided to measure heart rate variability (HRV), which is best measured over a minimum of two minutes (Camm et al., 1996), the verbal disgust clip was substituted for a longer clip taken from the series *The Anatomists* (Barker, 2002). The neutral clips were also edited to be 2 minutes long to meet the HRV requirement.

Self-reported emotion

Based on the questionnaire by Hornak et al. (2003; 1996), the *Subjective Emotional Change Questionnaire (SECQ)* asked individuals about their subjective experience of change in the intensity and frequency of experience of the emotions of amusement, anger, disgust, fear, happiness and sadness, since surgery. An additional question was added regarding the ability to express, describe, or distinguish between emotions (alexithymia). Responses were recorded as 0.5 *small change,* 1.0 *change,* or 1.5 *big change*.

After each film clip, participants rated their current mood on a computerized Visual Analogue Scale (VAS), shown on the same screen as the films. This comprised a vertical line for each of the target emotions. Participants rated the extent to which they felt each emotion by moving a cursor with a blue-tooth computer mouse.

Videorecording

All participants gave their consent to be videotaped during the film clips, using a Sony digital video camera placed above the LCD monitor. Five judges blind to condition and group membership rated the video recordings using a global rating method developed for this study (see Supplementary material). Judges rated the intensity with which the participants expressed each of the six target emotions during each film, as well as the frequency and intensity of verbal and nonverbal vocal expression, for a total of 14 ratings for 16 films. This method was found to have adequate inter-rater reliability (see Supplementary material). Vocal expressions were not analysed due to an insufficient number of vocalisations.

Physiological apparatus

Electrocardiogram (ECG) was recorded from a standard Einthoven Lead II using disposable *Meditrace* electrodes. All electrode impedances were below 50 k ohms. ECG signal was amplified using a 7P511 AC Grass amplifier. The amplified analogue signals were digitised at 1000 samples per second.

Procedure

The participant was seated in a testing room in a comfortable armchair 1 metre from a 56cm flat, widescreen, colour LCD monitor. The room was kept at a constant temperature of 22 degrees Celsius. Baseline resting ECG and EEG data (to be published separately) was recorded for 8 minutes with eyes open (O) and closed (C), using one of two randomly assigned counterbalanced orders. This baseline HR was used as a covariate in the analyses of HR during film clips.

Participants were shown two 1-minute practice film clips (one positive and one negative) to acclimatise to the experiment. For the experiment, film clips were randomly presented (using computer generated randomisation) within the constraints of the order of negative, neutral, negative, positive. This order was repeated four times for a total of 16 experimental clips. A 1-minute positive clip was shown after the final experimental clip to induce positive mood at the conclusion of the study.

Data reduction of ECG

ECG data from one control participant was lost due to technical issues. Participants who were currently taking medications that might alter autonomic function (e.g. antihypertensive or antiarrhythmic) were excluded from ECG analysis, resulting in the following group sizes: ACC n=4, orbital n=6, VM n=4, DL n=7, control n=20. Purpose-built software used an automated algorithm to detect ECG R waves, and calculate heart rate (HR) and heart rate variability (HRV) measures (de Zambotti, Nicholas, Colrain, Trinder and Baker, 2013; Trinder et al., 2001). Each recording was visually inspected for detection errors and manual adjustments for body movement artefacts were made where required. HR for each film clip was calculated by obtaining mean R-R interval over 5 second blocks. For assessment of HRV, the R-R interval time

series of artefact-free 2-minute epochs were extracted through a 2 second, 75% overlap Hamming window to prevent spurious estimates of spectral power. For each film clip, Fast-Fourier transformations were performed to derive estimates of spectral power in the low frequency (LF) band (0.04 – 0.15 Hz, in ms^2), which reflects a combination of sympathetic and parasympathetic nervous system input, and the high frequency (HF) band (0.15 to 0.4 Hz, in ms^2), which is a primarily parasympathetic measure. Raw power values were converted to normalized units [e.g. normalised LF = LF/(total power – very low frequency power) x 100, where very low frequency power= less than 0.04 Hz]. The ratio of low frequency to high frequency power (RLH) in ms^2 was calculated for each film clip by dividing LF/HF, which gave a measure of sympatho-vagal balance, whereby a smaller number indicates more dominant parasympathetic input (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996).

Global score calculation and statistical analyses

Given the large amount of data, it was necessary to collapse across emotions to reduce the number of statistical comparisons. Whilst emotions have been demonstrated to involve distinct neural systems, certain regions including the ACC and medial PFC are also involved in multiple emotions, including fear, disgust, anger, sadness, as well as positive emotions (see Etkin, Egner and Kalisch, 2011, for review). Importantly for our purposes, studies have found that positive and negative emotional reactions can be generally distinguished physiologically (e.g. Ekman, Levenson & Friesen, 1983) and in terms of self-reported affect, and facial expressions (e.g. Larsen, Norris & Cacioppo, 2003).

Global scores were calculated as follows: Mean positive response to positive films was calculated by adding the amusement and happiness ratings for each of the four positive film clips, and dividing this total by 8 (as there were two ratings for four film clips). Mean negative response to negative films was calculated by adding the anger, disgust, fear and sadness ratings for each of the eight negative films, and dividing this total by 32 (as there were four ratings for eight film clips). Mean positive and negative response to neutral clips was calculated in the same manner, using the neutral clips.

Mean HR during positive film clips was calculated by adding the mean HR during amusement and happiness clips, and dividing by two. Mean HR during negative film clips was calculated by adding the mean HR during anger, disgust, fear and sadness clips, and dividing by four. For HRV, LF, HF and RLH were calculated for each target emotion, averaged across verbal and non-verbal clips.

For facial expressions, mean intensity of target emotional valence during each discrete emotional film was calculated by adding the appropriate ratings for the verbal and nonverbal films, and dividing by the number of ratings. Then mean intensity of positive facial expressions during positive film clips was calculated by adding the mean value for positive facial expressions during amusement and happiness clips, and dividing by two. Mean negative facial expressions during negative film clips was calculated by adding the mean value for negative facial expressions during anger, disgust, fear and sadness clips, and dividing by four.

Analysis of variance analyses assessed differences between groups for self-reported emotion, facial expression and cardiac variables. For the SECQ, as per Hornak et al. (2003), a total score was calculated across all emotions, regardless of whether the change represented an increase or decrease. A priori Mann-Whitney tests compared each surgery group with the control group.

Significant group differences in lesion volume, WRAT-R standard score, TEA score and baseline HR presented potential confounding influences. To determine the impact of these variables and in line with previous research ([redacted] et al., 2014), supplementary analyses in the form of hierarchical regressions were calculated when significant group differences were found. Previous researchers have used simple correlations to achieve this aim (Hornak et al., 2003). However, given the finding of a significant correlation between VM lesion location and lesion volume, this approach was favoured as this calculates the proportion of unique variance that each variable contributes. Lesion location was entered in the first block of the hierarchical regressions (except for mean HR analyses, where baseline HR was entered first), ahead of lesion volume, WRAT-R standard score and TEA score in the subsequent block. As the aim of these analyses was to demonstrate that observed group differences were due to

differences in lesion location rather than in screening and baseline measures, no variables were removed from the regressions.

Results

Self-reported emotion

There were no significant differences between the control group and any of the surgery groups for mean positive affect, $F(4, 48)= 2.07$, $p= .10$, $\eta^2= .15$, or for positive ratings of neutral films $F(4, 48)= 0.28$, $p= .89$, $\eta^2= .03$, or negative ratings of neutral films $F(4, 48)= 0.56$, $p= .69$, $\eta^2= .05$. However, for mean negative affect, a univariate ANOVA found a significant group difference, $F(4, 48)= 3.28$, $p= .02$, $\eta^2= .22$. The VM group rated their emotions as significantly more negative than the control group following target negative clips, $t(29)= 2.79$, $p= .009$, depicted in Figure 2, which shows that the VM group scored higher than all other groups.

The VM group also scored significantly different from the OFC group, $t(10)= 2.26$, $p= .047$, but not significantly different from the ACC ($p= .12$) or DLPFC groups ($p= .18$).

(Figure 2 about here)

To determine whether this difference in negative affect for the VMPFC group was due to lesion location or lesion volume, a supplementary hierarchical regression was calculated. There was a significant regression model at both steps 1 ($R^2 =.22$, $p= .019$) and 2 ($R^2 =.27$, $p= .040$). In Step 1, VM lesion location was the only significant predictor of negative emotion in response to negative film clips, however there were no significant predictors at step 2, when lesion volume, WRAT-R standard score and TEA score were entered (see Supplementary material).

Facial expression

There was no significant group effect for negative facial expressions during negative film clips. However, an ANOVA found a significant effect of group for positive facial expressions during target positive film clips, $F(4, 48)= 2.57$, $p= .050$, $\eta^2= .18$. Figure 3 shows that the ACC, orbital and VM groups demonstrated less intense facial expressions of positive emotions during positive film clips. The difference between the orbital group ($M= 1.66$, $SD= 0.34$) and the control group ($M= 2.29$, $SD= 0.80$), just escaped significance, $t(31)= 2.02$, $p= .052$, $\eta^2= .08$. The VM group ($M= 1.70$, $SD= 0.38$) was also not significantly different from the control group, $t(29)= 1.61$, $p= .12$. However the DL group ($M= 2.52$, $SD= 0.81$) showed significantly greater positive facial expressions of emotion during positive film clips than both the orbital group, $t(14.55)= 3.13$, $p= .007$ and the VM group, $t(14)= 2.15$, $p= .050$.

(Figure 3 about here)

Table 2 shows the R^2 values and coefficients for the hierarchical regression for positive facial expressions during positive film clips. It can be seen that orbital lesion location was the only significant predictor of positive facial expression during positive film clips, even after the addition of lesion volume, WRAT-R standard score and TEA score.

(Table 2 here)

Heart rate

Mean HR

An ANCOVA found a significant effect of group for mean HR during positive emotional film clips, $F(4, 35)= 3.20$, $p= .024$, $\eta^2= .27$. The orbital group had a significantly lower mean HR during positive film clips ($M= 70.12$, $SE= 1.12$) than the

control group (M= 73.76, SE= 0.61), F(1, 23)= 8.14, p= .009, η^2= .26, after accounting for baseline HR.

(Figure 4 about here)

Table 3 shows the hierarchical regression model for mean HR during positive film clips. Baseline HR was the strongest predictor of HR during positive film clips, as shown by the large semi-partial correlation, however orbital lesion location was also a significant predictor of HR during positive film clips at steps 2 and 3.

(Table 3 about here)

An ANCOVA also found a significant effect of group for mean HR during negative emotional film clips, F(4, 35)= 3.49, p= .017, η^2= .29. A priori tests found that the orbital group had a significantly lower HR during negative film clips (M= 69.94, SE= 1.08) than the control group (M= 73.51, SE= 0.59), F(1, 23)= 8.42, p= .008, η^2= .27, after accounting for baseline HR (Figure 4, bottom panel).

A similar result was found for the hierarchical regression for HR during negative film clips, presented in Table 4, as baseline HR was again the strongest predictor, with orbital lesion location again also a significant predictor of HR at steps 2 and 3.

(Table 4 about here)

Heart rate variability during discrete target emotional film clips

For the low-frequency (LF) component of heart rate variability, the only significant group difference was found for happiness, F(4, 35)= 2.81, p= .040, η^2= .24. An a priori test found that the orbital group had significantly less LF than the control group, t(23)= 2.17, p= .041. Mean HRV values by group are shown in Table 5, which indicates that the orbital group tended to have smaller low frequency power values than

all groups for all emotions. It also shows that the VM group tended to have lower percentage of HF power than all other groups, however there were no significant differences in HF between controls and brain surgery groups for any of the emotions.

(Table 5 about here)

An ANOVA of RLH found a significant effect of group for the happiness target films, $F(4, 35)= 4.88$, $p= .003$, $\eta^2= .36$. A priori tests found that that the VM group had a significantly larger ratio than the control group $t(22)= 3.28$, $p= .003$. The VM group also had a significantly larger ratio than the control group for the disgust target films, $t(22)= 3.38$, $p= .003$ (Table 5).

Subjective emotional change

The orbital group reported significantly more subjective emotional change overall than the control group ($U= 32.50$, $p= .009$, $r= -.45$), with no other significant group differences observed.

The hierarchical regression for the total SECQ score is presented in Table 6. At step 1, orbital and DL lesion locations were significant predictors of SECQ total score, and the positive value of these standardised coefficients indicated that the presence of these lesions was associated with increased subjective emotional change. Orbital lesion location remained significant at step 2, however, DL lesion location was no longer significant. Instead, lesion volume was a significant predictor of total subjective emotional change, and suggested that as lesion size increased, so did subjective emotional change.

(Table 6 about here)

Discussion

The present study used film clips to elicit emotion in patients with surgical excision of the ACC, OFC, VMPFC or DLPFC and a control group of patients who had undergone spinal surgery, to ascertain the different contributions of the subregions of the VMPFC to emotional reactivity following VMPFC lesions. To our knowledge, this study is the first to attempt to experimentally elicit emotion in patients with surgically circumscribed lesions of the VMPFC in order to discern the functional contributions of its subregions in emotional reactivity.

The OFC group had a significantly lower HR for positive and negative clips, and significantly less low frequency power (reflecting a combination of sympathetic and parasympathetic components) during the target amusement clips than the control group. This is one of the first studies to report decreased cardiac autonomic drive during emotion elicitation in patients with lesions restricted to the OFC. These results support those of neuroanatomical studies that reported OFC connections to autonomic control areas including the hypothalamus and brainstem (reviewed in Rempel-Clower, 2007; Rolls, 1990). These results are also consistent with human studies that found autonomic changes following OFC stimulation (Chapman, Livingston, & Livingston, 1949; Livingston, Chapman, & Livingston, 1947), and functional neuroimaging studies that reported correlations between OFC activation and HR (Wager et al., 2009) and HRV during emotion elicitation (Lane, Reiman, Ahern, & Thayer, 2001).

Given the known anatomical connections of the MPFC to visceromotor control regions (Öngür & Price, 2000) in primates, it was unexpected that more significant differences on the psychophysiological variables were not observed in the ACC group. Whilst our sample size was identical to that of a previous similar study (Hornak et al., 2003), it's possible that the small size of the ACC group was responsible for a lack of power.

The VMPFC group had a significantly greater ratio of low to high frequency power compared to the control group for some of the film clips, this suggests greater dominant sympathetic input. Notably, this finding is in contrast to the decreased sympathetic power of the OFC group, even though patients with VMPFC lesions by definition had OFC involvement. Thus, while the OFC group showed reduced sympathetic activity, the VMPFC group had increased sympathetic activity, suggesting

that the impairments in emotional and social behaviour in patients with VMPFC lesions were not simply due to an additive effect of an OFC and MPFC lesion. Previous research has found increased cardiovascular activity in patients with VMPFC lesions. For example, a previous case report of a patient who sustained a lesion to the right OFC and ACC described how the patient had increased HR during positive and neutral emotional conditions (Angrilli, Palomba, Cantagallo, Maietti, & Stegagno, 1999). Another study reported paradoxical cardiovascular activation to emotional stimuli in patients with VMPFC lesions (Hilz et al., 2006), however only following right hemisphere VMPFC lesions.

As hypothesised, the DLPFC group showed a lack of significant differences from the control group. While the DLPFC is not generally considered part of the emotion network, patients with DLPFC lesions have been found to perform poorly on a reward-related task (Hornak et al., 2004), however the researchers argued that this was due to impaired attentional mechanisms. In the present study, the ceiling effect shown by this group on the TEA suggests that attention was not deficient in this group.

The OFC group reported significantly more subjective emotional change since their surgery on the SECQ, consistent with our hypothesis, however the VMPFC and ACC groups did not. The significant effect for the OFC group supports previous findings from human functional neuroimaging research indicating that the OFC is involved in the subjective experience of emotion (Anderson et al., 2003; Baker, Frith, & Dolan, 1997; Dougherty et al., 1999; Liotti et al., 2000; Pardo, Pardo, & Raichle, 1993). This result is also consistent with previous human lesion studies that found that the OFC is involved in the subjective experience of emotion (Berlin, Rolls, & Kischka, 2004; Hornak et al., 2003). Our finding does differ from that of Hornak et al. (2003) however, who concluded that bilateral OFC lesions are required for significant changes to subjective emotional state. Our results suggest that unilateral lesions are sufficient to cause such subjective changes. While the results from the SECQ support the argument that the OFC is important for the subjective experience of emotion, the results from the self-report ratings of emotion following film clips do not, as the OFC group didn't report altered self-reported emotion in response to the film clips compared to the control group. However,

the OFC group were rated as displaying less intense positive facial expressions during positive film clips.

Given the previous finding of reduced theory of mind and perception of facial emotion in the VMPFC group in a related study ([redacted] et al., 2014), and previous reports of blunted affect in patients with VMPFC lesions (Eslinger and Damasio, 1985; Barrash, Tranel and Anderson, 2000) it was unexpected that the VMPFC didn't have reduced self-reported emotion or reduced facial expression of emotion in response to film clips. Patients with VMPFC lesions have been reported to demonstrate a reduction in intensity of subjective experience of arousal (e.g. Tranel, Bechara, Damasio, & Damasio, 1998), however, their emotional disruption is variously expressed and interacts with environmental demands, as these patients have also been noted to display hyper-emotionality, including exaggerated emotional responses to immediately present stimuli (Anderson, Barrash, Bechara, & Tranel, 2006). In the present study, the VMPFC group did have higher self-rated negative affect in response to the films than the control group, which was opposite to the hypothesised direction; this however, was no longer significant when lesion volume, TEA and WRAT-R standard score were entered into the regression. Had this effect remained significant, it would have been consistent with findings of Anderson et al. (2006) who note that VMPFC lesioned patients can also display hyper-emotionality. Together the results of the previous ([redacted] et al., 2014) and present study suggest that while the OFC is more associated with the physiological and visceral response to emotion stimuli, the VMPFC may have a greater role in social cognition.

Our findings of reduced facial expression of emotion, sympathetic cardiac reactivity and increased subjective experience of emotion following OFC lesions in the present study support previous research suggesting that the OFC is involved in the subjective experience of emotion (Macefield, James, & Henderson, 2013). This is argued to be due to the role of the OFC in representing reward value and updating reward value associations between stimuli (Rolls, 2004).

The results of the present human lesion study make an important contribution to the literature regarding the roles of distinct subregions of the VMPFC in emotional reactivity, a literature that is primarily comprised of anatomical connectivity, animal lesion and human functional neuroimaging studies. The findings that we have presented

here, in combination with those of a previous study on social cognition in these patients ([redacted] et al., 2014) and known anatomical pathways, have led to a tentative model that requires future testing. This model suggests that when there is a discrete lesion to the MPFC, the intact OFC retains the signalling of emotional salience due to available representations of the reward value of stimuli (Rolls, 2004), and is able to inhibit inappropriate amygdala activity. Similarly, when there is a discrete lesion to the OFC, the intact MPFC remains able to perceive emotional salience due to consciously available emotion-related cognitions such as attention and self-reflection, and is able to inhibit inappropriate amygdala activity. In either instance, there will be some behavioural impairment, however this will be minor in comparison to when both areas are damaged. In patients with VMPFC lesions, not only is there a combined effect of deficits related to damage to the MPFC and the OFC, but the amygdala lacks sufficient inhibition, resulting in the behavioural syndrome of impairments in emotional and social functioning seen in patients with VMPFC lesions. This posited dual inhibition of the amygdala by the MPFC and OFC is a new explanation for the emotional and social disturbances of patients with VMPFC damage. However, in the absence of significant findings in the MPFC group in the present study, this model remains speculative pending further investigation.

Limitations and future directions

Whilst detailed, the present study was not without limitations. Although commonly used to infer changes in sympathetic and parasympathetic activity, interpretation of low frequency power has been suggested to reflect baroreflex function rather than purely cardiac sympathetic tone (Goldstein, Bentho, Park, & Sharabi, 2011). This highlights the need when studying emotion to measure reactivity across multiple channels, as in the present study, to achieve convergence and confidence in findings. Notwithstanding the challenges of recruiting suitable patients for the present study given that patients with discrete, surgically circumscribed lesions (particularly to the ACC) are rare, the sample size was somewhat limited. Thus although comparable to other studies in this area, the limited sample may explain the lack of findings for the ACC group. It should be further noted that patients with discrete, surgically circumscribed lesions of this area are rare. Nevertheless, even given the small group sizes, cautious interpretation of

the results is warranted, and while we found significant group differences, these results should be interpreted in the context of other lesion and neuroanatomical studies. Future lesion and neuroimaging studies are needed to test the dual inhibition model proposed, and would benefit from expanding our attempt to recruit participants from multiple sites, so that larger subgroups of patients with these uncommon, surgically circumscribed lesions may be included. Determining the precise roles of these distinct regions of the prefrontal and VMPFC has important implications for neurosurgery to these regions, not only for improving emotional and social outcomes in patients with lesions such as tumours or epileptic foci, but also for surgical intervention for psychiatric disorders, such as deep brain stimulation for treatment resistant depression.

Conclusion

We elicited emotion in a sample of patients with lesions to discrete regions of the PFC, including the MPFC and OFC, which are the two subcomponents of the VMPFC. The OFC group showed reduced sympathetic activity and the VMPFC group had increased sympathetic activity, suggesting that the impairments in emotional and social behaviour in patients with VMPFC lesions are not simply due to an additive effect of an OFC and MPFC lesions. The findings that the DLPFC group did not differ from the control group was in line with our hypothesis, however, we were surprised by the lack of significant findings for the MPFC group, however this may be due to the small sample size for this group. In addition to the finding of reduced sympathetic cardiac reactivity, the reduced facial expression of emotion and greater changes (which could be increases or decreases) in the subjective experience of emotion following OFC lesions in the present study support previous research suggesting that the OFC is involved in the subjective experience of emotion. The present study addresses a gap in the literature for human lesion research into the role of subregions of the VMPFC in emotion. We hope that our results will inform new theories and contribute to the development of treatments for emotional dysfunction.**References**

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Table 1 Demographic differences between groups

	ACC	Orbital	VM	DL	Control	Test
Gender M/F	2/2	3/4	3/2	5/6	12/14	p= .99
ESL Y/N	2/2	2/5	1/4	3/8	7/19	p= .91
Age (years)	M= 38.00, SD= 11.58	M= 53.43, SD= 8.00	M= 51.80, SD= 16.74	M= 45.64, SD= 17.52	M= 45.69, SD= 13.95	F(4, 48)= 0.96, p= .44, η^2= .07
Days post-surgery	M= 142.25, SD= 145.19	M= 125.71, SD= 105.71	M= 141.60, SD= 125.11	M= 149.91, SD= 129.70	M= 98.81, SD= 77.15	F(4, 48)=0.61, p= .66, η^2= .05
Years education	M= 11.75, SD= 0.50	M= 12.57, SD= 3.91	M= 12.20, SD= 1.79	M= 13.68, SD= 3.51	M= 12.69, SD= 3.88	F(4, 48)= 0.31, p= .87, η^2= .03

Note. ESL= English is second language.

Table 2 Hierarchical Regression for Positive Facial Expressions during Positive Film Clips

		B	*SE B*	β	*t*	*p*	Zero-order Correlation	Semi-partial correlation
Step 1	***R*²= .18***							
	Constant	2.29	0.14		16.16	.00***		
	ACC lesion	-0.54	0.39	-.19	-1.40	.17	-.16	-.20
	Orbital lesion	-0.63	0.31	-.28	-2.05	.05*	-.26	-.28
	VM lesion	-0.59	0.35	-.23	-1.68	.10	-.20	-.24
	DL lesion	0.23	0.26	.12	0.88	.38	.24	.13
Step 2	***R*²= .19**							
	Constant	1.19	4.54		0.26	.80		
	ACC lesion	-0.63	0.46	-.22	-1.35	.18	-.16	-.18
	Orbital lesion	-0.72	0.33	-.32	-2.16	.04*	-.26	-.29
	VM lesion	-0.83	0.69	-.32	-1.21	.23	-.20	-.16
	DL lesion	0.13	0.30	.07	0.45	.66	.24	.06
	Lesion volume	0.00	0.00	.20	0.96	.34	-.09	.13
	WRAT-R	0.00	0.01	-.05	-0.32	.75	.01	-.04
	TEA score	0.21	0.61	.08	0.35	.73	.21	.05

Note. *p< .05, **p< .01, ***p< .001.

Table 3 Hierarchical Regression for Mean Heart Rate during Positive Film Clips

	B	*SE B*	β	*t*	*p*	Zero-order Correlation	Semi-partial correlation

Step 1	R^2= .93***							
	Constant	-0.84	4.71		-0.18	.86		
	Baseline HR	1.03	0.07	0.93	15.75	.00***	.93	.93
Step 2	R^2= .95***							
	Constant	-3.76	4.71		-0.82	.42		
	Baseline HR	1.07	0.06	0.97	17.02	.00***	.93	.91
	ACC lesion	-0.83	1.65	-0.03	-0.50	.62	.07	-.03
	Orbital lesion	-3.56	1.40	-0.14	-2.54	.02*	-.14	-.14
	VM lesion	3.05	1.75	0.10	1.75	.09	-.21	.09
	DL lesion	0.92	1.32	0.04	0.69	.49	.11	.04
Step 3	R^2= .95***							
	Constant	19.64	20.93		0.94	.36		
	Baseline HR	1.12	0.08	1.01	14.52	.00***	.93	.78
	ACC lesion	-2.81	2.10	-0.10	-1.34	.19	.07	-.07
	Orbital lesion	-4.33	1.54	-0.17	-2.81	.01**	-.14	-.15
	VM lesion	0.43	3.11	0.01	0.14	.89	-.21	.01
	DL lesion	0.26	1.43	0.01	-0.18	.86	.11	.01
	Lesion volume	0.00	0.00	0.04	0.38	.71	-.04	.02
	WRAT-R	-0.08	0.06	-0.09	-1.35	.19	.21	-.07
	TEA score	-2.65	3.00	-0.09	-0.88	.38	.31	-.05

Note. *p< .05, **p< .01, ***p< .001.

Table 4 Hierarchical Regression for Heart Rate during Negative Film Clips

	B	*SE B*	β	*t*	*p*	Zero-order	Semi-partial

							Correlation	correlation
Step 1	R^2= .94***							
	Constant	-4.56	4.39		-1.04	.31		
	Baseline HR	1.08	0.06	.94	17.69	.00***	.94	.94
Step 2	R^2= .96***							
	Constant	-6.95	4.24		-1.64	.11		
	Baseline HR	1.11	0.06	.97	19.19	.00***	.94	.91
	ACC lesion	-1.06	1.52	-.04	-0.70	.49	.06	-.03
	Orbital lesion	-3.51	1.29	-.14	-2.72	.01**	-.13	-.13
	VM lesion	2.49	1.61	.08	1.55	.13	-.24	.07
	DL lesion	1.13	1.22	.05	0.93	.36	.12	.04
Step 3	R^2= .96***							
	Constant	0.36	19.89		0.02	.99		
	Baseline HR	1.12	0.07	.98	15.30	.00***	.94	.76
	ACC lesion	-1.63	1.99	-.05	-0.82	.42	.06	-.04
	Orbital lesion	-3.72	1.46	-.14	-2.54	.02*	-.13	-.13
	VM lesion	1.10	2.96	.04	0.37	.71	-.24	.02
	DL lesion	0.95	1.36	.04	0.70	.49	.12	.03
	Lesion volume	0.00	0.00	.03	0.32	.76	-.06	.02
	WRAT-R	-0.01	0.06	-.01	-0.23	.82	.26	-.01
	TEA score	-0.94	2.85	-.03	-0.33	.74	.35	-.02

Note. *p< .05, **p< .01, ***p< .001.

Table 5. Mean Percentage of Spectral Power Values During Discrete Target Emotional Film Clips by Group.

		Group														
Emotion	Value	ACC			Orbital			VM			DL			Control		
		High	Low	Ratio L/H	High	Low	Ratio L/H	High	Low	Ratio L/H	High	Low	Ratio L/H	High	Low	Ratio L/H
Amusement	Mean	23.11	74.88	4.17	29.03	57.89	3.18	20.89	76.55	4.26	22.92	66.34	4.96	22.88	71.20	4.55
	SE	6.12	9.29	1.72	5.00	7.59	1.40	6.12	9.29	1.72	4.63	7.02	1.30	2.74	4.16	0.77
Anger	Mean	26.75	71.31	3.12	35.93	48.59	1.93	24.09	72.94	3.86	31.00	58.21	2.51	31.34	62.35	3.29
	SE	6.98	9.13	1.12	5.70	7.46	0.91	6.98	9.13	1.12	5.27	6.90	0.84	3.12	4.08	0.50
Disgust	Mean	33.99	63.13	2.01	37.53	48.87	3.03	19.70	77.90	5.99	34.27	54.50	2.19	32.21	61.86	2.57
	SE	7.03	9.02	1.22	5.74	7.36	0.99	7.03	9.02	1.22	5.31	6.82	0.92	3.14	4.03	0.55
Fear	Mean	33.64	64.11	2.04	35.52	48.71	2.00	24.34	72.15	4.57	32.02	58.58	2.51	29.79	64.55	2.91
	SE	5.78	8.71	1.06	4.72	7.12	0.87	5.78	8.71	1.06	4.37	6.59	0.80	5.84	3.90	0.48
Happiness	Mean	34.31	63.05	2.29	39.35	45.23	1.73	14.48	83.36	7.44	30.24	56.92	2.59	28.65	65.64	3.19
	SE	6.44	9.00	1.07	5.76	8.05	0.95	6.44	9.00	1.07	4.87	6.80	0.81	2.88	4.02	0.48

Sadness	Mean	31.00	66.56	2.47	34.29	51.99	2.42	19.91	77.64	4.91	32.35	55.32	2.24	29.62	64.65	2.88
	SE	6.44	8.86	0.91	5.25	7.23	0.74	6.44	8.86	0.91	4.86	6.69	0.68	2.88	3.96	0.41

Table 6. Hierarchical Regression for Total Subjective Emotional Change Questionnaire Score.

		B	*SE B*	β	*t*	*p*	Zero-order Correlation	Semi-partial correlation
Step 1	R^2= .17							
	Constant	1.62	0.34		4.73	.00***		
	ACC lesion	0.89	0.94	.13	0.95	.35	.03	.13
	Orbital lesion	2.03	0.74	.38	2.74	.01**	.29	.36
	VM lesion	0.89	0.85	.14	1.04	.30	.04	.14
	DL lesion	1.29	0.63	.29	2.07	.05*	.17	.27
Step 2	R^2= .26*							
	Constant	6.79	10.39		0.65	.52		
	ACC lesion	0.18	1.06	.03	0.17	.86	.03	.02
	Orbital lesion	1.66	0.76	.31	2.17	.04*	.29	.28
	VM lesion	-1.79	1.58	-.29	-1.13	.26	.04	-.15
	DL lesion	0.90	0.68	.20	1.33	.19	.17	.17
	Lesion volume	0.00	0.00	.44	2.20	.03*	.30	.28
	WRAT-R	-0.01	0.03	-.03	-0.19	.85	-.08	-.02
	TEA score	-0.67	1.40	-.11	-0.48	.64	-.11	-.06

Note. *p< .05, **p< .01, ***p< .001.

Figure 1

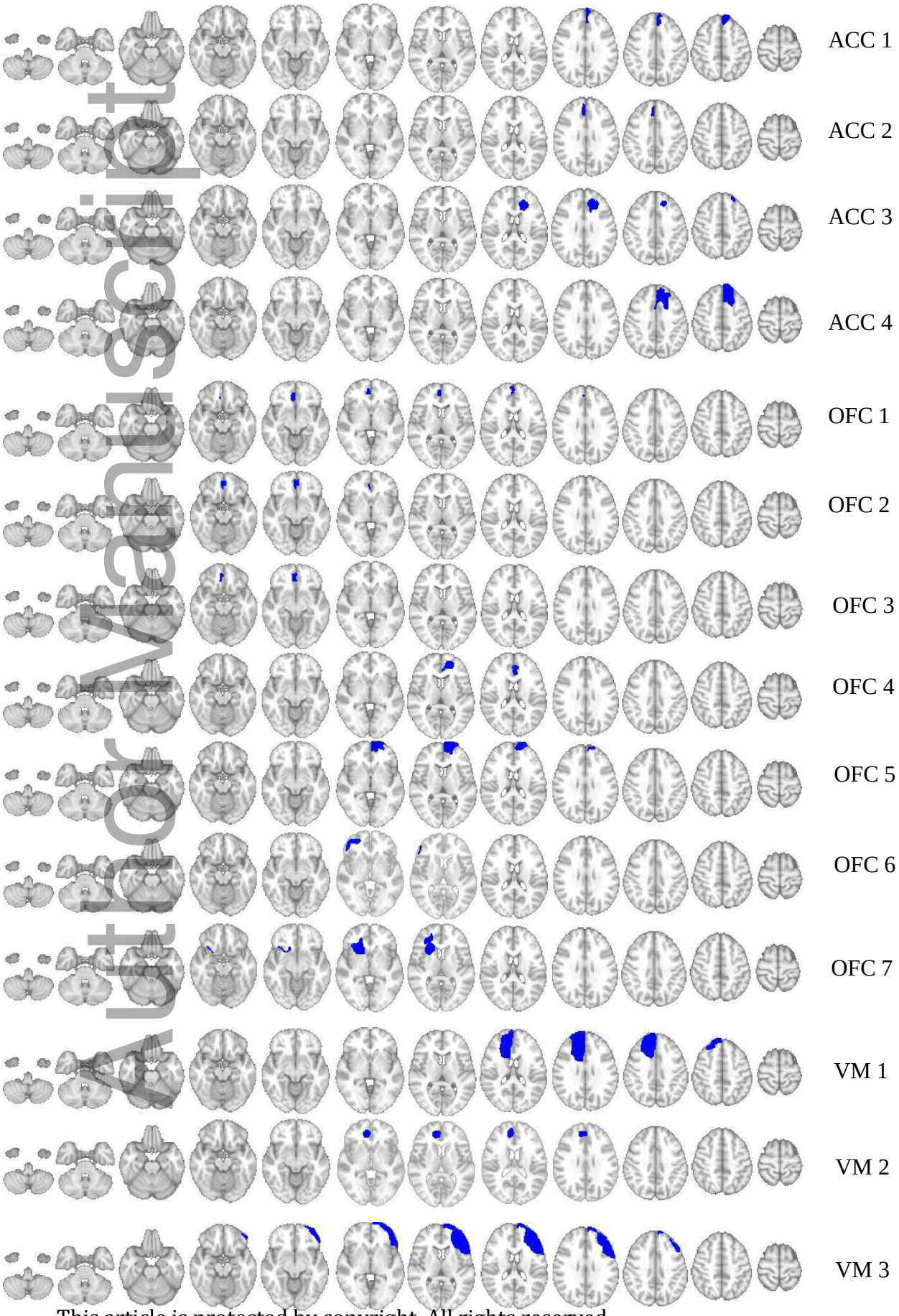

Figure 1 (continued)

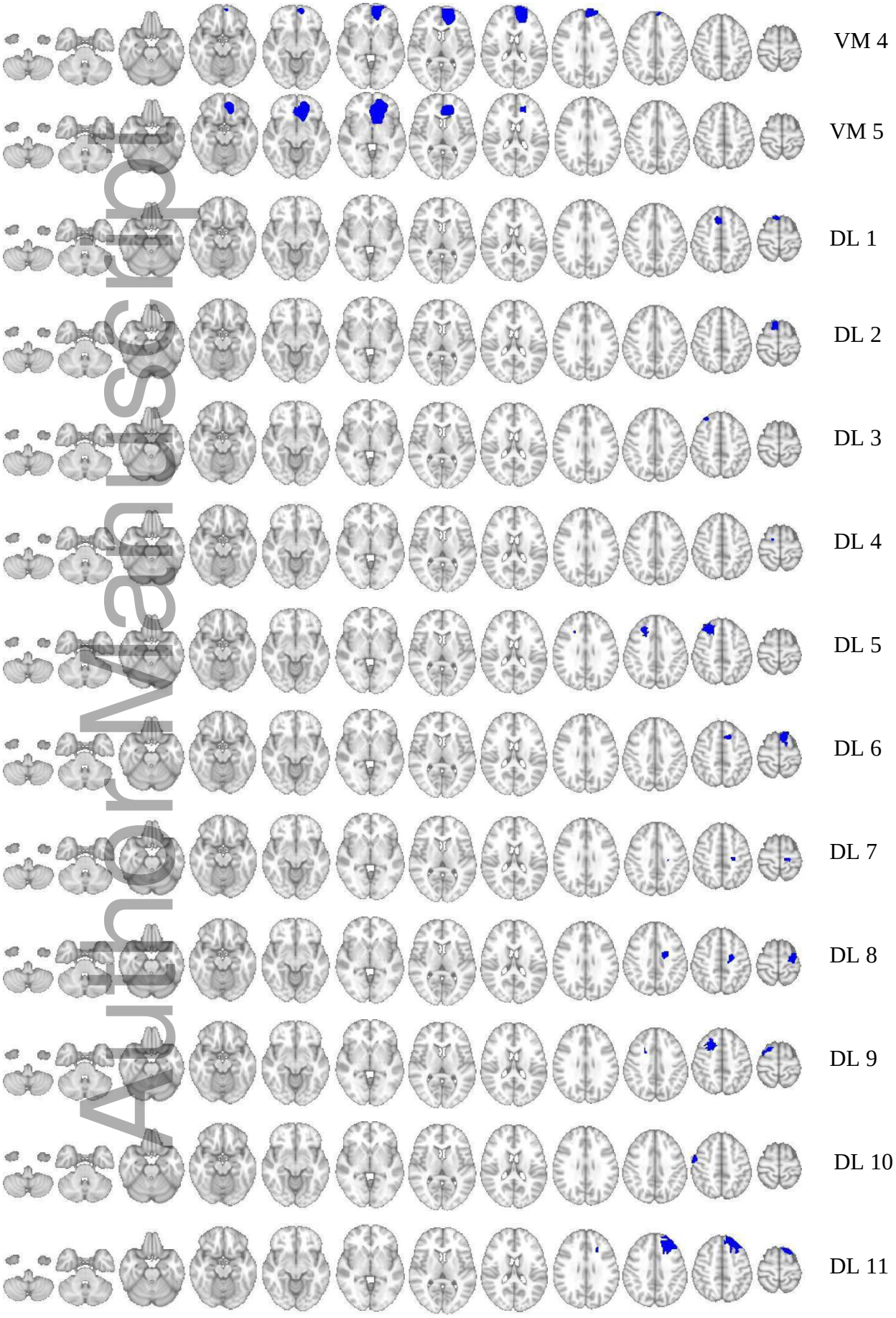

Figure 2

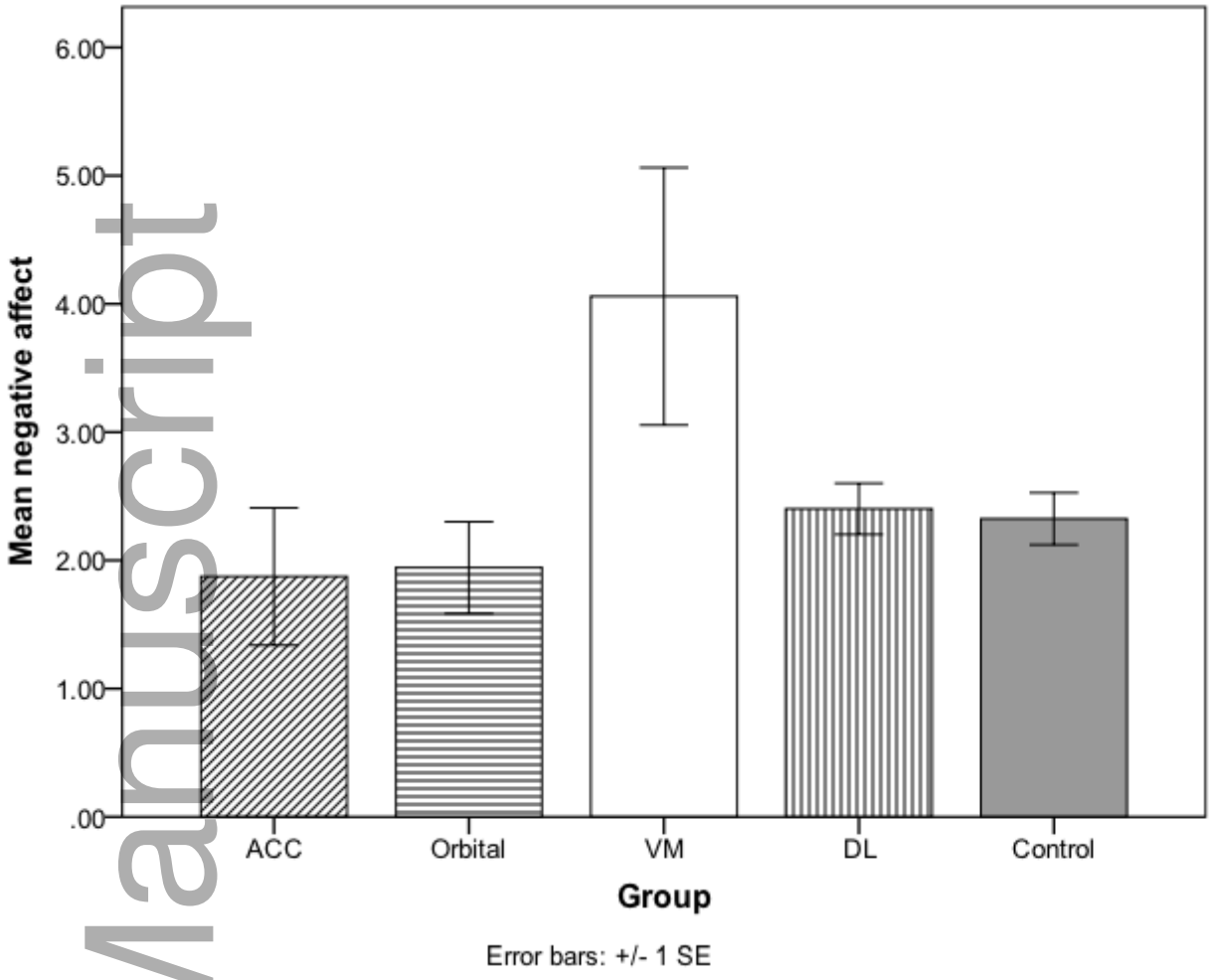

Figure 3

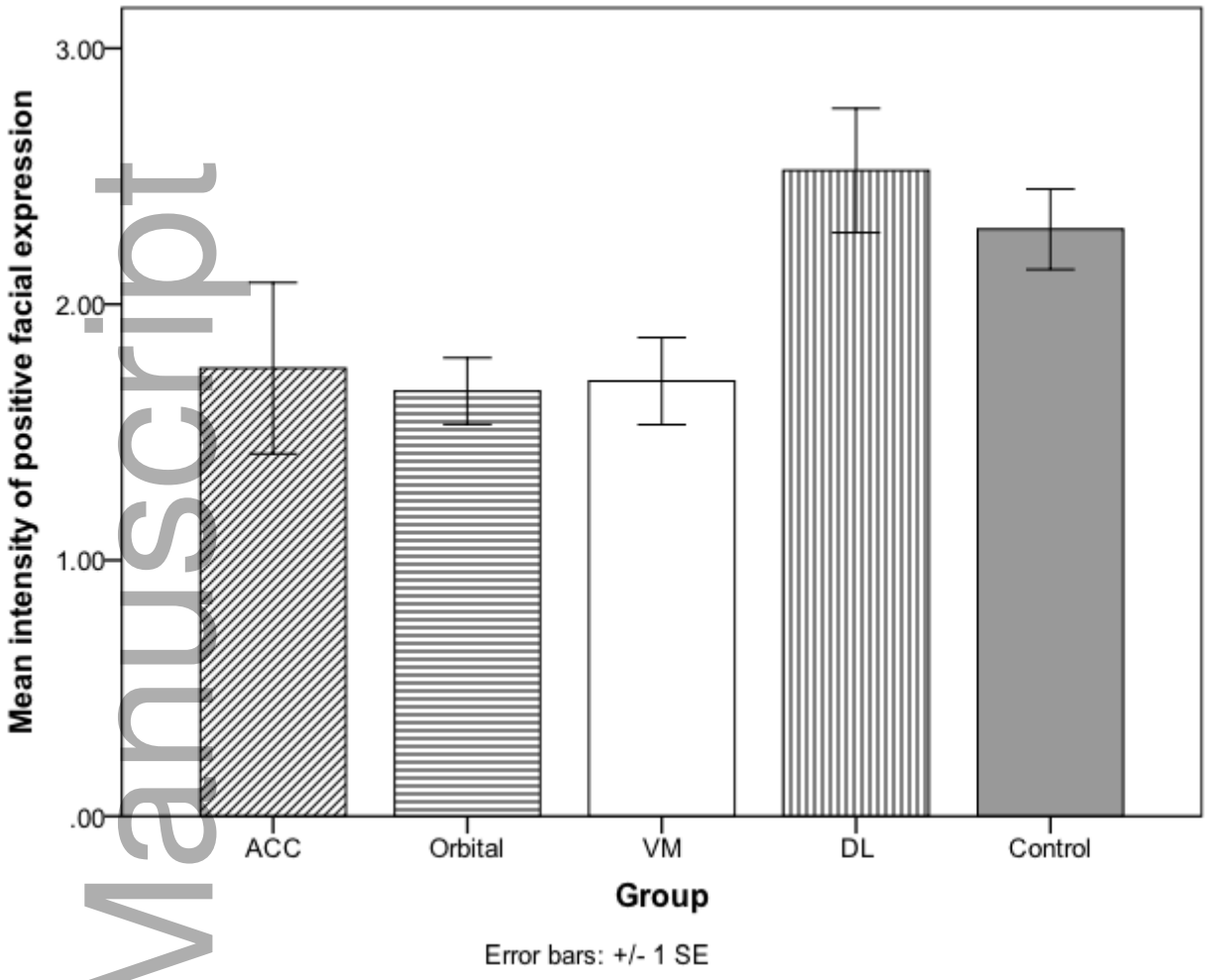

Figure 4