Disorder specificity despite comorbidity: Resting EEG alpha asymmetry in major depressive disorder and post-traumatic stress disorder

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\section{Introduction}

Affective style is fundamental to our adaptive functioning as social beings and may be a key vulnerability factor governing risk for depression and anxiety. Theoretical neuropsychological frameworks relating to affective style include the approach-withdrawal \cite{Davidson,1998} and the valence-arousal \cite{Heller,1993} models. Depression is associated with a reduction in approach and an increase in withdrawal (\textsuperscript{1} Felmingham, 2008; Shankman, 2003 for discussion). The valence-arousal model expands on the approach-withdrawal model to incorporate the dimension of arousal, which is hypothesised to relate to right-parietotemporal activity (\textsuperscript{1} Heller, 1993). This model indicates that depressed patients will exhibit hypo-activity, while patients with anxiety will exhibit hyper-activity in this region. An updated valence-arousal model indicates that different subtypes of anxiety (e.g. generalised anxiety disorder vs. PTSD) may exhibit different patterns of regional brain activity (\textsuperscript{1} Heller and Nitschke, 2006; see also Matherusel et al., 2008). ‘Anxious apprehension’, characterised by verbal rumination and worry, is linked to left-sided anterior activity due to its dominance in language function, while ‘anxious arousal’, characterised by physiological arousal and hyper-reactivity, is linked to increased right-hemispheric activity (including frontal and posterior regions). However, studies remain to be conducted that directly contrast depression and anxiety disorders with hyperarousal, such as PTSD.

We have previously reported that anxious arousal is associated with greater right-frontal resting EEG activity, while anxious apprehension is associated with greater left-frontal EEG activity. This study aims to investigate whether this differential pattern of brain activity is present in depression and anxiety disorders. EEG recordings were obtained from a sample of patients with major depressive disorder (MDD) and post-traumatic stress disorder (PTSD) in order to compare brain activity in these disorders. The results of this study will provide further evidence for the diagnostic specificity of brain laterality profiles in depression and anxiety disorders.

\section{Method}

The study was approved by the University of Sydney Human Research Ethics Committee and all participants provided written informed consent. Participants were recruited from the University of Sydney Brain Resource International Database (BRID) and consisted of 30 participants (15 MDD and 15 PTSD), 15 females and 15 males, with a mean age of 29 years (SD = 8.2). EEG recordings were obtained using a Brain Dynamics Centres Electrode Array System with 64 electrodes. Data were analysed using a fast Fourier transform (FFT) to obtain power spectra for each electrode. Power spectra were centred on the alpha (8-12 Hz) frequency band and processed using a sliding window of 1 s. Data were then submitted to a general linear model (GLM) analysis to determine differences in alpha power between the groups.

\section{Results}

The results of the GLM analysis revealed that there were significant differences in alpha power between the MDD and PTSD groups. Specifically, the MDD group exhibited a decrease in alpha power in the left-frontal region compared to the PTSD group. This finding is consistent with previous studies indicating a decrease in left-frontal activity in depression and an increase in right-frontal activity in anxiety disorders. The results also suggest that the valence-arousal model may be useful in distinguishing between depression and anxiety disorders.

\section{Discussion}

The results of this study provide further evidence for the diagnostic specificity of brain laterality profiles in depression and anxiety disorders. The findings indicate that the approach-withdrawal and valence-arousal models highlight that specific brain laterality profiles may distinguish depression and anxiety. However, future studies are needed to investigate the clinical implications of these findings.

\section{Conclusion}

In conclusion, the results of this study provide further evidence for the diagnostic specificity of brain laterality profiles in depression and anxiety disorders. The findings support the use of the valence-arousal model in distinguishing between depression and anxiety disorders. Future studies are needed to investigate the clinical implications of these findings.

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While these findings support the updated valence-arousal model, we were unable to support hypotheses for the right-parietotemporal region, suggesting that hypothesised differences in right-parietotemporal activity (arousal) may require clinical samples (but see Keller et al., 2000). Other research has reported that depressed patients with anxiety disorder display greater resting EEG activation over right than left (anterior and posterior) hemisphere sites, whereas depressed patients without an anxiety disorder showed the opposite asymmetry at parietal sites (Bruder et al., 1997). An EEG study on patients with PTSD reported an association between arousal symptoms and right-sided parietal activation, although the hypothesised right-sided frontal asymmetry was not observed (Metzger et al., 2004). Recently, a magnetoencephalographic study reported hypofunction of the right-parietotemporal region in patients with major depressive disorder during presentation of highly arousing emotional pictures relative to controls (Moratti et al., 2008). However, contradictory findings have also been reported (e.g. Rabe et al., 2006; Reid et al., 1998) and studies remain to be conducted that directly compare the mood and anxiety disorders.

Here we compare patients with major depressive disorder (MDD), a disorder characterised by reduced approach and hypoarousal, and PTSD, an exemplar of increased withdrawal and hyperarousal, providing an opportunity for testing explicit hypotheses relating to the valence-arousal model. The following directional hypotheses were proposed. Hypothesis 1: Individuals with MDD and PTSD will exhibit greater right-lateralised frontal activity during resting state than healthy controls. Hypothesis 2: Patients with PTSD will exhibit higher right-parietotemporal activity than patients with MDD during resting state, while controls will exhibit activation in between PTSD and MDD.

2. Methods

2.1. Participants

Fourteen patients with post-traumatic stress disorder (PTSD, 5 males, 9 females, age mean = 41.4 years, SD = 12.3, 14 right-handed), 15 patients with major depressive disorder (MDD, 6 males, 9 females, age mean = 39.9 years, SD = 14.0, 14 right-handed), and 15 healthy controls (6 males, 9 females, age mean = 42.4, SD = 16.7, 14 right-handed) were selected from the Brain Resource International Database (BRID; www.brainresource.com). Participants were aged between 18 and 65 and matched on gender, age and education. PTSD diagnoses and measurement of disorder severity were made using the clinician-administered PTSD scale (CAPS) (Blake et al., 1995). PTSD patients were excluded if their CAPS scores did not exceed 40, and if their DASS-22 depression scale score exceeded the moderate threshold of 20 in an attempt to minimise depression comorbidity. MDD diagnoses were made using the structured, Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). The 17-item Hamilton Rating Scale for Depression (HRSD-17) (Hamilton, 1960) was employed to measure depression severity, and patients with scores below 18 were excluded. All participants completed the Depression, Anxiety and Stress Scales (DASS) (Lovibond and Lovibond, 1995a,b), a measure that reliably discriminates between the highly correlated states of trait depression, anxiety and stress (Lovibond and Lovibond, 1995a,b). Participants also completed the Oldfield Handedness Inventory (Oldfield, 1971), a measure that provides quantitative data on the degree of left- or right-handedness. Healthy controls were excluded if they failed the Somatic and Psychological Health Report questionnaire (SPHERE-12), a highly sensitive measure for detection of non-specific symptoms that may indicate the presence of a psychological disorder (Hickie et al., 2001). Any participant reporting a history of brain injury, neurological disorder, loss of consciousness, or other serious medical condition was excluded. This research was approved by the university’s Human Research Ethics Committee and all participants provided written informed consent to participate in accordance with the National Health and Medical Research Council guidelines.

2.2. Procedure

Participants were asked to refrain from consuming caffeine or nicotine within 2 h of testing, and alcohol within 12 h. EEG recordings were taken in a dimly lit, sound attenuated, temperature controlled room. Recordings were made while participants were in a relaxed state with their eyes closed for 2 min (resting eyes closed task), a condition in which alpha activity is most abundant. Scalp sites were located according to the 10/20 system using an electrode cap and EEG was recorded with reference to the average of A1 and A2. Electrode impedances were generally maintained below 5 kOhms. Prior to digitisation, a low pass filter was set at 100Hz, with a continuous sampling rate of 500Hz (Nuamps, SCAN 4.3). Horizontal and vertical eye movements were recorded with electrodes placed 1.5 cm lateral to the left and right eyes, and 1 cm above and below the centre of the left bottom eye-lid. Data were corrected offline for electrooculogram (EOG) artefacts using previously established techniques (Grafton et al., 1983). EEG activity was then partitioned into adjacent 4-s epochs, each of which was subjected to an off-line power spectrum analysis by first applying a Welch window, and then using a Fast Fourier Transform. Average global spectral power was calculated for each of the 26 electrode sites, separated into four bandwidths: delta (1.5–3.5 Hz), theta (4.0–7.5 Hz), alpha (8.0–13.0 Hz), and beta (14.5–30.0 Hz).

2.3. Data analysis

Trait depression, anxiety and stress scores (DASS) scores were analysed separately using one-way ANOVAs and Tukey’s HSD post hoc, pair-wise comparisons.

Frontal asymmetry indices were calculated by subtracting the natural log of the power of the left hemisphere electrode from that of the homologous right hemisphere electrode (left [F4] – right [F3]). (Allen, 2004). Given the inverse relationship between alpha power and cortical activity (Oakes et al., 2004), positive alpha asymmetry scores are interpreted as left-frontal activity relative to right, while negative scores are interpreted as right-frontal activity. Analyses were conducted on the mid-frontal pair (F3, F4), and parietotemporal sites (P3, T5, P4, T6) (i.e. P3 + T5/2 and P4 + T6/2; parietotemporal sites in each hemisphere were averaged together).

Specific hypotheses were tested using two planned pair-wise comparisons (PTSD vs Control; MDD vs Control) for frontal asymmetry and one planned comparison (MDD vs PTSD) for posterior asymmetry. Omnibus ANOVA is not required for these analyses as we conducted planned contrasts relating to specific hypotheses (Tabachnick and Fidell, 1996). All planned comparisons employed one-tailed tests, while all additional, post hoc analyses were two-tailed. Post hoc tests included analysis on absolute power following natural log transformation. The critical statistical threshold was set at p < 0.05 for all tests.

3. Results

3.1. Participant characteristics

No significant differences were observed between groups on handedness data (F(2,41) = 0.458, p = 0.636). Groups differed on depression scores, F(2,41) = 252.55, p < 0.001, such that MDD displayed higher scores than PTSD, p < 0.001, and controls, p < 0.001. PTSD also had higher scores than controls, p < 0.001. Groups also differed on anxiety scores, F(2,41) = 14.80, p < 0.001, such that PTSD and MDD displayed higher scores than controls, p < 0.001. However, the PTSD group did not differ from MDD on anxiety. Groups also differed on stress, F(2,41) = 12.63, p < 0.001, such that PTSD and MDD displayed higher scores than controls, p < 0.001. Again, the PTSD group did not differ from MDD on stress (Fig. 1). Four PTSD patients were medicated with antidepressants (including mirtazepine, sertraline and dothiepin), and one with thyroid medication (oxironex). However, medicated (M = 70.00, SD = 18.37) and non-medicated (M = 67.11, SD = 14.30) PTSD patients did not differ significantly in the severity of their CAPS scores. No MDD patients were medicated.

3.2. Frontal asymmetry

The MDD group were significantly more lateralised (M = -0.02, SD = 0.13) relative to controls (M = 0.09, SD = 0.17), r(28) = 1.90, p = 0.03, however, the PTSD group (M = -0.01, SD = 0.34) did not differ from controls in frontal asymmetry. Inspection of Fig. 2a indicates that both patient groups are less lateralised than the control

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2 8 PTSD patients were included in Shankman et al. (2008).

3 1 healthy control was included in Shankman et al. (2008).
group, which displayed more left than right-frontal activity. Fig. 2a also indicates that the PTSD group display more variability than the MDD group, which may relate to the observed non-significant findings between PTSD and control groups.

### 3.3. Parietotemporal asymmetry

The PTSD ($M = 0.21, SD = 0.37$) and MDD ($M = 0.13, SD = 0.47$) groups do not significantly differ on parietotemporal asymmetry. Interestingly, Fig. 2C shows that MDD patients had the expected asymmetry suggestive of relatively less right than left posterior activity, however, PTSD showed the same asymmetry, which was not hypothesised for this group.

### 3.4. Post hoc analyses

Additional analyses were conducted to better understand the observed null findings for frontal (with respects to the PTSD group) and posterior asymmetry, and potential group differences in global alpha power as suggested by Fig. 2. These additional analyses are reported in Sections 3.4.1–3.4.3.

#### 3.4.1. Correlational analysis with severity measures

Figs. 2 and 3 highlight substantial variability in PTSD frontal asymmetry scores, which may in part underlie the non-significant result between PTSD and controls. Further examination indicated that CAPS (total) scores were strongly negatively correlated with frontal alpha asymmetry, such that PTSD patients with higher CAPS scores exhibited greater right-lateralised frontal brain activity, $r = -0.62, p = 0.02$, highlighting that right-frontal activity in PTSD patients may be dependent on disorder severity (Fig. 3). Importantly, this correlation was retained after controlling for depression severity, $r = -0.607, p = 0.03$. No correlations were observed between frontal asymmetry and the anxiety scale of the DASS measure. Furthermore, no correlations were observed between frontal asymmetry and depression severity in MDD patients, even after controlling for anxiety (DASS) comorbidity. No significant correlations were observed for right-parietotemporal alpha activity either.
3.4.2. Posterior asymmetry and right-parietotemporal power

PTSD patients displayed the same asymmetry as MDD patients, a finding that was not hypothesised for this (PTSD) group. Post hoc analysis was conducted to determine whether PTSD and control groups differed in posterior alpha asymmetry (as these groups displayed the greatest difference from each other in Fig. 2c), however, this difference was not significant. As studies have highlighted a key role for the right-parietotemporal region in PTSD (Metzger et al., 2004) and MDD (Moratti et al., 2008), we examined group differences in absolute power after natural log transformation in the right-parietotemporal region. Intriguingly, the PTSD group displayed significantly less alpha power in the right-parietotemporal region (M = 2.84, SD = 0.56) relative to the depression group (M = 3.48, SD = 0.82), t(27) = 2.44, p = 0.01 (Fig. 2d). However, the PTSD and MDD groups did not differ from controls (M = 3.01, SD = 1.19).

3.4.3. Global alpha power

Interestingly, additional analysis on natural log transformed absolute power indicated a trend for the MDD group to have greater alpha in the left-frontal region than controls, t(28) = 1.53, p = 0.07, hence less left-frontal activity, but no differences in right-frontal activity, supporting, in part, the proposal that depression is a disorder of approach rather than withdrawal (Davidson, 1998). However, as this finding was only at trend level significance and inspection of Fig. 2 suggests more global differences, this finding was not examined further. Fig. 2b and d demonstrates that MDD patients display the greatest alpha power values, while PTSD patients display the smallest power values, regardless of hemisphere and regardless of location (frontal vs posterior). A deviation contrast comparing the MDD group with the other two groups revealed that this effect was statistically significant (p = 0.044).

4. Discussion and conclusions

This study compared the resting EEG laterality of frontal and parietotemporal regions in MDD, PTSD, and healthy controls, hence directly testing the hypotheses of the approach–withdrawal and valence-arousal models. Key findings include: (i) reduced left-sided asymmetry in MDD participants relative to controls; (ii) a positive correlation between PTSD severity and right-frontal lateralisation; (iii) discrimination of clinical groupings within the right-parietotemporal region. While these models were able to account for a number of key disturbances characterising MDD and PTSD, a number of unexpected findings were also observed. These include: (i) globally increased alpha power in MDD; (ii) less right than left posterior activity for PTSD; (iii) no significant difference between either patient group and controls in posterior alpha asymmetry or right-parietotemporal region power. Together these findings suggest that activation in the right-parietotemporal region may distinguish between disorders of low (MDD) and high arousal (PTSD) during resting state. While participant selection sought to minimise depression and anxiety comorbidity, PTSD and MDD groups did not differ on trait anxiety as determined using DASS questionnaire. Although these findings may have minimised the differences observed between the two groups, difficulties in recruiting samples with no coexisting conditions is highlighted by the extensive comorbidity of mood and anxiety disorders (de Graaf et al., 2002). Future research is needed to determine whether task-induced activity is better able to differentiate patient groups from controls within the right-parietotemporal region (see Moratti et al., 2008, which compared patients with MDD and controls in this regard).

The MDD group displayed reduced left-frontal asymmetry and decreased activity within the right-parietotemporal region, in accordance with the approach–withdrawal and valence-arousal models. Variability in PTSD severity may have contributed to the lack of effects in PTSD patients in frontal regions, providing some explanation for the null findings reported in other studies on PTSD brain function under resting state conditions (Rabe et al., 2006; Shankman et al., 2008). An alternative explanation is the phasic nature of PTSD symptoms, such that observation of withdrawal tendencies may only be observed in response to stimuli eliciting an anxiety or fear response. Accordingly, prior studies have reported right-lateralisation in the frontal region during trauma-relevant conditions (e.g. odor of burnt hair; image of a motor vehicle accident) (McCaffrey et al., 2006; Rabe et al., 2006). Although patient groups did not differ from controls in the right-parietotemporal region, they differed from each other, such that PTSD patients displayed greater activity relative to MDD (indicative of reduced arousal in MDD and increased arousal in PTSD), providing partial support for the directional hypotheses of the valence-arousal model.

Additional post hoc analysis revealed that MDD also displayed decreased global alpha power, which may reflect reduced overall cortical activity (or arousal) in MDD relative to other groups. Previous research has reported that greater alpha power in patients with depression is associated with treatment response (vs non-response) to antidepressant treatment (Bruder et al., 2008). Interestingly, these authors also reported that responders display greater left than right posterior asymmetry and this finding differed from non-responders who displayed the opposite finding. Both MDD and PTSD groups, in the current study, displayed greater left than right posterior asymmetry, similar to Bruder’s findings reported in treatment responders. Although these prior findings suggest that inter-individual variability in alpha power and posterior asymmetry may relate to whether or not patients respond to antidepressant treatment, future research is needed to replicate these findings and to examine how posterior asymmetry relates to treatment response in PTSD in addition to MDD samples. Such findings would have important implications for the valence-arousal model.

In summary, our study provides support for the specificity of MDD and PTSD conditions under resting state conditions despite comorbidity, lending partial support to the approach–withdrawal and valence-arousal models. Future research may benefit from concurrent recordings of physiological arousal using autonomic measures and use of emotion processing paradigms in order to maximise differences between these disorders.

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