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The impact of melancholia versus non-melancholia on resting-state, EEG alpha asymmetry:

Electrophysiological evidence for depression heterogeneity

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Abstract

While depression has been associated with relatively greater right than left frontal cortical activity – a neurophysiological marker reflecting greater activation of the withdrawal system – contradictory findings have been reported. It was hypothesised that melancholia would be associated with relative right frontal activation, in comparison to non-melancholia and controls. We collected 2-minutes of resting-state, eyes closed, electroencephalographic activity from a total of two hundred and thirty seven participants including 117 patients with major depressive disorder (57 with melancholia, 60 with non-melancholia) and 120 healthy controls. In contrast to hypotheses, patients with non-melancholia displayed relative left frontal activation in comparison to controls and those with melancholia. These findings were associated with a small to moderate effect size (Cohen's $d = 0.30 - 0.34$). Critically, patients with melancholic subtype did not differ from controls despite increased severity – relative to those with non-melancholia – on clinical measures. These results may reflect an increase in approach tendencies in patients with non-melancholia including reassurance seeking, anger or irritable aggression. Findings highlight the need for further research on the heterogeneity MDD.

Keywords: depression, melancholia, non-melancholia, electroencephalography, EEG, alpha asymmetry

1. INTRODUCTION

Neurophysiological models of affect (Harmon-Jones, Gable and Peterson, 2010; Kemp and Felmingham, 2008) have associated relatively greater left than right frontal cortical activity to approach-related motivation, and relative right frontal activation to withdrawal. While relative right frontal activation (reduced approach and / or increased withdrawal) has been reported in depressed samples, (e.g. Thibodeau et al., 2006), studies have reported contradictory findings including relative left frontal activation (e.g. Minnesh et al., 2004; Segrave et al., 2011). One explanation for discrepant findings is that major depressive disorder (MDD) is a heterogeneous disorder characterised by distinct subtypes including melancholic and non-melancholic depression.

The majority of studies on this topic have used electroencephalography (EEG) – focusing on the alpha bandwidth (8-13Hz) in particular – to examine frontal brain activation. Alpha power in the resting state may be interpreted as an index of neural inactivity, while power suppression reflects active cognitive processing (Pfurtscheller et al., 1996)¹. More recently, neuroimaging studies have reported that high alpha power is associated with low brain metabolism (Laufs et al., 2003; Moosmann et al., 2003; Oakes et al., 2004). Here we examine alpha asymmetry during resting state to index approach versus withdrawal motivational tendencies in patients with melancholia and non-melancholia relative to controls.

We have previously examined the impact of MDD on this measure (Kemp et al., 2010) reporting reduced left frontal activation and increased global alpha power in patients with MDD relative to controls, findings interpreted as reduced approach motivation and generalised cortical deactivation, respectively. However, melancholia may be characterised by anxiety, arousal and

¹More recent research has demonstrated that EEG alpha power may increase under certain conditions such as withholding or controlling response execution (Cooper et al., 2003; Klimesch et al., 2007). This event-related synchronisation may reflect top-down inhibitory processes. The present study however, focuses on the alpha during resting state and our interpretation of alpha is consistent with prior research in this regard (see (Harmon-Jones, Gable & Peterson, 2010 for review).

hypercortisolemia (Gold and Chrousos, 2002), features associated with relative right frontal activation (Kemp et al., 2010; Mathersul et al., 2008; Heller et al., 1997; Engels et al., 2007). By contrast, non-melancholia is associated with worry or anxious apprehension (Parker et al., 2012); a feature associated with relative left frontal activation (Mathersul et al., 2008; Heller et al., 1997; Engels et al., 2007). Here we examine the impact of melancholia versus non-melancholia on EEG alpha asymmetry in the absence of emotion provocation during an eyes-closed resting state. It was hypothesised that melancholia would be associated with relative right frontal activation, as compared to patients with non-melancholia and controls.

2. METHODS

2.1. Participants:

One hundred and seventeen patients with a primary diagnosis of major depressive disorder (MDD) and 120 healthy control participants were obtained from the Brain Resource International Database (Gordon et al., 2005). Participants did not have any history of brain injury (causing loss of consciousness for 10 minutes or more), neurological disorder, other serious medical condition, or substance abuse / dependence greater than 1 year. All participants were medication free for at least 5 half-lives. Healthy control participants did not have a self-reported history or presence of psychiatric illness. All participants gave written informed consent in accordance with National Health and Medical Research Council (NHMRC) ethical guidelines.

Patients met criteria for MDD as determined by trained and supervised research officers using the Mini International Neuropsychological Interview (MINI: Sheehan et al., 1998), a structured psychiatric interview based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. Patients were then sub-grouped for melancholia (MEL; N = 57) or non-melancholia (NMEL; N = 60) on the basis of the MINI, and these groupings were confirmed and

validated using the CORE Assessment of Psychomotor Change (CORE; Hickie, 1996), a measure that supports diagnostic classification into melancholia and non-melancholia. The self-report, Depression, Anxiety and Stress Scales (DASS; Lovibond and Lovibond, 1995) was also completed.

2.2. Procedure:

Electrophysiological (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 minutes. EEG was recorded from 26 sintered Ag-AgCl electrodes positioned according to an extension to the 10/20 international system mounted in an elastic cap. Data was recorded relative to a virtual ground – due to specific hardware requirements – and then referenced offline. The choice of reference is a divisive issue among EEG researchers (Davidson et al., 2000; Allen et al., 2004). Here we report findings from data referenced to both the average of A1 + A2 (ear reference; ER) and average activity at all recorded EEG sites (average reference; AR). Impedances were generally maintained below 5k Ω . A low pass filter was set at 100Hz prior to digitalization, with a continuous sampling rate of 500Hz (NuAmps, SCAN 4.3). Horizontal and vertical eye movements were recorded with electrodes placed 1.5cm lateral to the left and right outer canthi, 3mm above the centre of the left eyebrow, and 1.5cm below the centre of the left bottom eye-lid. Data were corrected offline for electrooculogram (EOG) artifacts using previously established techniques (Miller et al., 1988; Gratton et al., 1983). The data was corrected for artifact using four methods: eye blink correction; threshold based artifact rejection for all analyses; ERP specific rejection criteria; manual data rejection. The following criteria were used for artifact rejection: voltage threshold (any epoch that has a voltage level above 100 μ V on at least 3 channels was rejected); the number of bad channels for rejection (if more than 50% of the epochs are rejected, then the entire analysis is marked bad).

EEG was divided into adjacent intervals of four seconds, which were then subjected to spectral power analysis by first applying a Welch window to the data, and then performing a Fast Fourier Transform (FFT). The power spectra were averaged for each electrode position, and power was then calculated for the alpha bandwidth (8-13 Hz). Power data were log transformed in order to better approximate the normal distribution, an assumption required by parametric statistical methods. Absolute power was examined following the recommendations of Pivik et al. (1993). Frontal asymmetry scores were calculated on the alpha bandwidth by subtracting the power of the left hemisphere electrode from that of the homologous right hemisphere electrode (i.e. F4 – F3) and the parietotemporal asymmetry scores were calculated by subtracting the average of one left parietal and one temporal electrodes from that of the average of the homologous electrodes of the right hemisphere (i.e. $[P4+T6/2] - [P3+T5/2]$).

2.3. Statistical Analyses

All statistical analyses were performed using SPSS (Version 20: SPSS Inc, Chicago). Significant effects were set at $p < 0.05$ (two-tailed), while findings were labelled as trends if $p < 0.1$ and $p > 0.05$. Repeated measures ANOVAs were conducted on alpha asymmetry scores: Group (MEL, NMEL, CTRL) x Region (frontal, parietotemporal). Main and interaction effects of group were analysed using post-hoc, pairwise, between-group comparisons with the Tukey correction for multiple comparisons.

3. RESULTS

3.1. Participant Characteristics

There were no significant differences for group on gender ($\chi^2 (2, N = 238) = 1.386, p = 0.238$), age ($F(2, 235) = 1.876, p = 0.155$) or handedness ($\chi^2 (2, N = 238) = 3.551, p = 0.169$). MEL and NMEL

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groupings differed significantly on CORE total score ($t(90.042) = 4.205, p < 0.001$) providing an important validation of diagnostic categorisation. As expected, significant differences were also observed between groups (melancholia, MEL; non-melancholia, NMEL; controls, CTL) on interviewer rated depression severity (HRSD; $F(2, 235) = 970.578, p < 0.001$), self-reported depression (DASS-D; $F(2, 235) = 453.578, p < 0.001$), self-reported anxiety (DASS-A; $F(2, 235) = 98.497, p < 0.001$) and self-reported stress (DASS-S; $F(2, 235) = 235.543, p < 0.001$) such that MEL displayed more severity on all measures relative to NMEL and CTL respectively. NMEL also displayed more severity than CTL on these measures. In addition to a primary diagnosis of MDD, secondary diagnoses included generalised anxiety disorder ($n = 45$), panic disorder ($n = 29$), posttraumatic stress disorder ($n = 14$) and substance abuse ($n = 33$). MEL was characterised with more diagnoses of panic disorder only ($\chi^2(1, N = 117) = 7.775, p = 0.005$).

3.2. EEG Alpha Asymmetry

Main effects of group were observed regardless of region, for data based on the averaged (A1 + A2) ear reference ($F(2, 234) = 3.588, p = 0.029$) as well as for data based on the average reference ($F(2, 234) = 3.709, p = 0.026$). Post hoc tests revealed that NMEL display a relative global left-hemispheric activation (across frontal and parieto-temporal regions) (Fig 1a) relative to CTL (Tukey HSD, $p = 0.026$, for the ear reference) and MEL (Tukey HSD, $p = 0.022$, for the average reference). MEL did not differ from CTL. On the basis of a priori predictions for effects within the frontal regions in particular, frontal asymmetry data was further inspected at frontal (Fig 1b) and posterior (Fig 1c) regions separately (see Figure 1b and 1c). Interestingly, results indicated a significant one-way ANOVA for group in frontal ($F(2, 235) = 3.273, p = 0.040$ for ear reference; $F(2, 235) = 3.354, p = 0.097$ for average), but not posterior regions. Post hoc tests revealed that NMEL display relative left frontal activation (Fig 1b) relative to CTL (Tukey HSD, $p = 0.065$, Cohen's $d = 0.30$, for the ear reference)

and MEL (Tukey HSD, $p = 0.056$, Cohen's $d = 0.34$, for the ear reference; Tukey HSD, $p = 0.084$, Cohen's $d = 0.33$, for the average reference). MEL did not differ from CTL. Severity, DASS, nor CORE scores correlated with asymmetry measures.

[INSERT FIGURE 1]

4. DISCUSSION

In contrast to our hypotheses, patients with non-melancholia, not melancholia, differed from controls on EEG alpha asymmetry. More specifically, patients with non-melancholia displayed relative left frontal activation in comparison to controls, interpreted as increased approach tendencies. Intriguingly, relative left frontal activation has been associated with depression among high reassurance seekers (Minnex et al., 2004). Anger and irritable aggression – negatively valenced, approach-related motivations – have also been linked to relative left frontal activation (Harmon-Jones, 2003) and patients with non-melancholia may be more prone to such behaviours (Parker, 2000; Parker et al., 2002). While it is also possible that the relative left frontal activation observed in patients with non-melancholia relates to worry or anxious apprehension, we found no associations between stress – a measure consistent with anxious apprehension – and alpha asymmetry in the current sample. Thus, relative left frontal activation observed in patients with non-melancholia may be related to negative, approach-related, emotional states. Critically, while melancholic patients were rated as more severe on clinical measures, they did not differ from controls on frontal alpha asymmetry.

Although our findings were unexpected, our study is characterised by a number of strengths including a relatively large sample size, a medication free sample, and control for age, gender and handedness. However, our study also had a number of limitations. Firstly, for pragmatic reasons, the duration of the recorded EEG was relatively short. Secondly, spectral power analysis was based on four-second epochs; typical studies have conducted analysis on 2-second segments (Cacioppo et al.,

2007). While it is possible that our unexpected findings reported here could be due to methodological issues, we consider this unlikely. We have previously reported that 2-minutes of eyes-closed EEG alpha produced high test-retest reliability (Williams et al., 2005) and high internal consistency (Cronbach's Alpha reliability estimates ranged from 0.969 to 0.991) (Mathersul et al., 2008). In fact, estimation of spectral features on recordings as short as 60 seconds are reliable (Cacioppo et al., 2007). In addition, although studies have analysed shorter epoch lengths (1 – 2 seconds) to avoid violating the stationarity assumption (Gasser and Molinari, 1996), segments double this length still meet this assumption in spontaneous EEG recordings (Cacippo et al., 2007).

It is possible that the findings obtained from patients with non-melancholia relate to a combination of approach-related tendencies including reassurance seeking, anger and irritable aggression. While it is unclear why patients with melancholia did not differ from controls on alpha asymmetry – especially considering that these patients reported more severe depression, anxiety and stress – it is interesting to note that a meta-analysis of EEG studies (Thibodeau et al., 2006) on patients with comorbid depression and anxiety was inconclusive (i.e. the mean weighted effect size did not differ significantly from zero). One possible explanation for these findings on comorbid samples is that anxiety and stress have differential effects on alpha asymmetry: while anxiety (arousal) is associated with relative right frontal activation and increased withdrawal, stress (anxious apprehension and worry) is associated with relative left frontal activation. In this regard, relative left frontal activation may reflect a verbal component mediated by left-hemispheric language functions (Engels et al., 2007; Heller et al., 1997). While stress (anxious apprehension) did not correlate with relative left frontal activation in the current study, we (Mathersul et al., 2008) and others (Engels et al., 2007) have reported this finding previously in independent samples. In summary, our study provides further support for conceptualising depression as a heterogeneous disorder and highlights the need for further research on subtypes of depression to increase homogeneity in patient samples.

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Figure 1: Figures display alpha asymmetry score \pm standard error by group regardless of region (top; Fig 1a), within the frontal region (middle; Fig 1b) and parieto-temporal region (bottom; Fig 1c). P-values correspond to pairwise comparisons based on Tukey HSD. CTLS: controls; NMEL: patients with non-melancholia; MEL: patients with melancholia

