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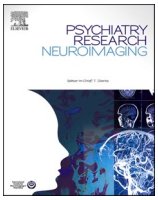

Alpha wave asymmetry is associated with only one component of melancholia, and in different directions across brain regions

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ABSTRACT

Alpha wave asymmetry inconsistently correlates with Major Depressive Disorder (MDD). One possible reason for this inconsistency is the heterogeneity of MDD, leading to study of depressive 'subtypes', one of which is Melancholia. To investigate the correlation between Melancholia and alpha-wave asymmetry, 100 community participants (44 males, 56 females; aged at least 18 yr) completed the Zung self-rated Depression Scale, and underwent 3 min of eyes closed EEG recording from 24 scalp sites. There was no significant correlation between EEG data and Melancholia total score for the entire sample, but there was for those participants who had clinically significant depression (n = 33). When examined at the level of individual Melancholia scale items, significant EEG data correlations were found for some of the items but not for others. Factor analysis revealed a two-factor structure for the Melancholia scale, only one of which exhibited significant correlations with EEG AA data. Further exploration of those data identified two subcomponents of that Melancholia factor, one which was inversely correlated with frontal alpha asymmetry, and another which was directly correlated with parietal-occipital alpha wave asymmetry. These findings suggest that Melancholia may itself be heterogeneous, similarly to MDD, and rely upon different aspects of cognitive function.

1. Introduction

1.1. Depression

As well as being intrinsically unpleasant, depression makes the largest contribution to global disability (WHO, 2017). Unfortunately, current first-line treatments are only about 35% effective alone, and about double that when combined (Rush et al., 2006; Thornicroft et al., 2017), and one the reasons for this limited efficacy may be the heterogeneity of depression (Ostergaard et al., 2011; Parker, 2005). Consequently, several 'subtypes' of depression have been described (Chekroud et al., 2017; Luedtke and Kessler, 2021), one of which is 'Major Depressive Disorder with Melancholic Features' (APA, 2022), or 'Melancholic depression' (Parker et al., 1996), referred to here as 'Melancholia'.

1.2. Melancholia

Melancholia has typically been characterized by the presence of several of the diagnostic criteria for Major Depressive Disorder (MDD) plus several other unique symptoms. MDD symptoms present in Melancholic depression include: anhedonia, despair/empty mood, and psychomotor agitation or agitation; unique symptoms in Melancholic depression are: a lack of reactivity to usually pleasurable events, depression usually worse in the morning, waking at least two hours before usual waking time, significant weight problems, and excessive guilt (APA, 2022).

However, precise definition (and diagnosis) of Melancholia "has long evaded attempts at accurate definition" (Parker and McCraw, 2017, p. 133), and its diagnosis has been the subject of some dispute (Tondo et al., 2020). One significant model of Melancholia was argued by Parker and colleagues (1990; 1994), who developed a sign-based scale ('CORE') for distinguishing melancholic from non-melancholic depressed patients

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(for a review of 57 studies of the CORE, see: Parker and McCraw, 2017). A further development from the same research team produced the Sydney Melancholic Prototype Index (SMPI), which was shown to be effective in distinguishing melancholic from non-melancholic participants in a community sample, principally based upon scores for anhedonia, low energy, loss of interest, impaired concentration, lack of improvement in mood/being able to be cheered up, and thoughts of death/suicide, and also associated with severity of depression (Parker et al., 2019).

1.3. Neural correlates of melancholia

These (and other) studies provide some basis for assessing Melancholia in a systematic way within community samples. From that, it is reasonable to attempt to identify neural correlates of Melancholia as a possible biomarker, as well as a potential pathway for increased understanding of the nature of this variant of depression. One neural correlate of general depression is alpha asymmetry (AA), with previous research reporting greater alpha activity in left frontal brain sites than in right frontal brain sites, but some evidence of the opposite effect in the parietal lobes (i.e., greater alpha activity in right parietal sites than in left parietal sites) (Bruder et al., 2017). However, apart from some initial findings regarding melancholic patients' EEG patterns, that review noted that the clinical heterogeneity of depression had yet to be conclusively examined for its effect on AA, although there was some evidence that abnormal perceptual asymmetry and ERP hemispheric asymmetry were relatively common among melancholic patients. Further, and as noted more recently by Bruun et al. (2021), more than four decades of research into this issue has focused almost exclusively on EEG-based data produced from three types of studies: sleep EEG studies ($n = 10$), event-related potentials (ERP) studies ($n = 9$), and just five studies of EEG resting state. Although each type of study provided some evidence that EEG data could be used to distinguish between Melancholia/non-Melancholia and control participants, there was considerable heterogeneity in methodology, particularly within the resting state studies, where "choice of methodology, analysis, and outcome variables of interest differed markedly between the five studies" (Bruun et al., 2021, p. 6). Additionally, sample sizes of participants were relatively small, ranging from 10 to 57 for these resting state studies. The largest of these studies (Quinn et al., 2014) focused on AA, but reported no significant differences between melancholic and control participants in AA collected from the frontal regions. Of the two other studies reviewed by Bruun et al. (2021) that focused on AA, one did not compare melancholic and non-melancholic participants (Kano et al., 1992), and the other failed to find significant differences between these two subgroups (Pizzagalli et al., 2002) using data from the frontal regions. Thus, the lack of clarity regarding the association between Melancholia and AA remains a limitation in understanding the neurophysiology of Melancholia and potentially developing reliable biomarkers for this subtype of MDD.

1.4. Research issues

From Bruder et al. (2017) and Bruun et al. (2021)'s reviews of this field, two research issues need attention when considering the associations between Melancholia and EEG alpha asymmetry. First, the valid identification of melancholic participants; and second, the recruitment of participant samples of sufficient size to provide adequate statistical power to reject null findings. The first of these issues may be addressed by reference to Parker et al. (1994; 2019) findings for their melancholic and community samples, described in section 1.2. Application of those characteristics that were found to discriminate between melancholic and non-melancholic participants (i.e., anhedonia, low energy, loss of interest, impaired concentration, lack of improvement in mood/being able to be cheered up, thoughts of death/suicide, and severity of depression) represents a valid method of identifying participants with Melancholia. The second issue (statistical power) is amenable to *a priori* calculation based upon use of a correlation coefficient statistical approach to detect meaningful associations between Melancholia and EEG alpha asymmetry. Both of these methods were followed here, allowing for an investigation of the associations between Melancholia and EEG alpha asymmetry within a community sample that included participants with a range of depression severity, and who were able to be divided into 'depressed' versus 'non-depressed', and then investigated for their associations between Melancholia and EEG alpha asymmetry.

One further issue that is of potential value in understanding and treating Melancholia is whether the acknowledged heterogeneity of depression (Milaneschi et al., 2020; Ostergaard et al., 2011) also applies to Melancholia that is based upon multiple symptoms (Parker et al., 1994, 2019). The limitations of applying dichotomous classification systems (i.e., melancholic vs non-melancholic) and the necessary use of ANOVA models to compare such groups (Cohen, 1983) were also considered here, leading to the application of correlational statistics instead of ANOVA to enable testing of the range of possible levels of depression and Melancholia severity and their association with EEG asymmetry.

1.5. Study aims

Therefore, this study aimed to extend understanding of the neurophysiological correlates of Melancholia, defined by reference to a multisymptom model previously validated within psychiatric and community samples (i.e., Parker et al., 1990, 1994, 2019). Specifically, EEG alpha asymmetry was measured for its correlation with a total score for Melancholia, and also for scores on individual Melancholia symptoms. It was hypothesized that Melancholia scores would be significantly correlated with EEG alpha asymmetry, and that this association would be influenced by overall depression severity.

2. Materials and methods

2.1. Participants

Because the effect of depression severity on the association between Melancholia and EEG alpha asymmetry was an aspect of the study, *a priori* power analysis was undertaken to determine the necessary sample size of depressed participants necessary for a reliable correlational analysis. To test for the presence of a moderate level correlation (i.e., at least $r = 0.3$: Cohen, 1988), with alpha = 0.05 and power of at least 0.80) a sample of 33 depressed participants was required. These were drawn from a previously-described community sample of 100 community participants (44 males, 56 females) (Sharpley et al., 2023) consisting of adults over the age of 18 years from the New England region of New South Wales, using the exclusion criteria of no previous medical history of severe physical brain injury, previous brain surgery, or past or current history of epilepsy or seizure disorder. Although some previous research into alpha asymmetry and depression has used handedness of participants as a selection criteria, that was not done here because a recent meta-analysis of over 35,000 individuals across 87 studies failed to find any meaningful effect on depression due to handedness (Packheiser et al., 2021). Further, there is no certainty that left hemispheric dominance is determined entirely by right-handedness, as evidenced by the finding that 60% to 70% of left-handed people also have left hemispheric dominance (Segalowitz and Bryden, 1983)

2.2. Instruments

2.2.1. Background questionnaire

Participants responded to questions about their age (years) and sex.

2.2.2. The self-rating depression scale (SDS)

Melancholia Subscale. The 20-item SDS (Zung, 1965) includes the

Diagnostic Criteria and several Associated Features of the most recent definition of Major Depressive Disorder (APA, 2022). Respondents indicate the frequency of each of the 20 SDS items by answering: 'None or a little of the time' (scored as 1), 'Some of the time' (2), 'Good part of the time' (3), or 'Most or all of the time' (4), providing total raw scores from 20 to 80 (used in this study). SDS raw scores of 40 or above indicate the presence of "clinically significant depression" (Zung, 1973, p. 335). The SDS has demonstrated split-half reliability of 0.81 (Zung, 1965), 0.79 (DeJonge and Baneke, 1989) and 0.94 (Gabrys and Peters, 1985), and internal consistency (alpha) of 0.88 for depressed patients and 0.93 for non-depressed patients (Schaefer et al., 1985). The SDS total score was used to classify participants into 'depressed' versus 'non-depressed' on the basis of Zung's cutoff score of at least 40. In addition to the 20 SDS items, the item "I do not feel much better even when good things happen" was included in a Melancholia scale consisting of the SDS items shown in Table 1. This item, plus the SDS items shown in Table 1, were used to calculate a Melancholia score for participants (Parker et al., 1994, 2019).

2.3. EEG data

Participants refrained from caffeine or other substances that may have influenced their concentration and/or psychophysiological state in the 12 h prior to their EEG recording. EEG data were collected using a 40-channel Digital EEG Amplifier (NuAmps), and a *Quick Cap* with electrodes, during 3 mins Eyes Closed resting condition. Participants' hair had been washed with a normal shampoo before the EEG session. After preparing the skull, electrode sites were cleaned with *Nuprep* gel, plus an alcohol swab, and the cap and electrodes were applied, making sure that the Cz electrode was located at a site half way between the glabella and the inion. Participants sat in an experimental booth and their EEG signals were acquired and recorded using the *Curry 7* software.

Using the five-percent electrode system described by Oostenveld and Praamstra (2001), depicted in Fig. 1, 24 active homologous EEG channels were used in this study (Frontal lobe electrodes: FP1, FP2, F3, F4, F7, F8, FT7, FT8, FC3, FC4; Temporal lobe electrodes: T7, T8, TP7, TP8, C3, C4; Parietal lobe electrodes: P3, P4, CP3, CP4: Parietal-Occipital lobe electrobes: PO1, PO2; and Occipital lobe electrodes: O1, O2). Referencing electrodes were the ground electrode (GND), the Central electrodes (Fz, FCz, Cz, CPz, Oz), Ear (Auricle) electrodes (A1, A2), the Horizontal Electro-Occulographic electrodes (X2, X4) and the Vertical Electro-Occulographic electrodes (X1, X3). The Electro-Occulographic electrodes were used for monitoring horizontal and vertical eye movements, and for off-line eye-movement artefact reduction of the EEG data.

Data were collected at a sampling rate of 1 KHz, with the frequency band set to collect alpha wave activity using online low and high filters of 8 Hz and 13 Hz respectively. Allowable impedance level was < 5 kΩ for each electrode, using the extended 10–20 electrode placement system (Oostenveld and Praamstra, 2001) and the CAR (Common Average Referencing) referencing style. Data were processed using a band pass filter with a low filter (high pass) frequency of 1 Hz and a slope of 2 Hz; a high filter (low pass) with frequency of 30 Hz and a slope of 8 Hz; a notch filter of 50 Hz (Harmonics) with a slope of 1.5 Hz; and a band stop filter of frequency of 50 Hz (Harmonics) with a width of 10 Hz and slope of 5 Hz. Data tapering was done using a Hann window with a 10% width to prevent data loss. EEG data were visually examined to identify artefacts (eye movements, muscle movements, spontaneous discharges, or electrode pops, etc.), which were then removed from the data record. Bad block and eye blink detection (using the magnitude of eye blink deflections as a set threshold criterion to detect artefacts) was undertaken by three automated methods (Subtraction, Covariance and Principal Component Analysis) to produce clean EEG data.

Back-to-back epochs of 4 s duration were then created from the cleaned EEG data, excluding epochs with bad blocks. Spectral analysis was performed on the generated epochs with a Fast Fourier Transformation to calculate the power spectra, which were averaged across the 4-second EEG epochs to produce the total power within the alpha (8–13 Hz) frequency range for each participant. The values of the total power within the alpha frequency range were then extracted and transferred to an SPSS file for statistical analysis. Alpha asymmetry was calculated from the log transformed alpha power values obtained from corresponding cerebral sites, i.e., LogRight α minus LogLeft α, and referred to herein as 'AA', to produce 12 sets of AA data.

Table 1
Melancholia symptoms and items used in Melancholia scale.

Melancholia symptoms[1]	Item
Anhedonia	I still enjoy sex[2] (R)
Low energy	I get tired for no reason[2]
Loss of interest	I still enjoy doing the things I used to do[2] (R)
Impaired concentration	My mind is as clear as it used to be[2] (R); I find it hard to make decisions[2]
Thoughts of death/suicide	I feel that others would be better off if I was dead[2]
	I feel that I am useful and needed[2] (R)
Lack of improvement in mood/able to be cheered up	I do not feel much better even when good things happen[3]

[1] Based on Parker et al. (1994, 2019)
[2] SDS item
[3] Item derived from Parker et al. (1994, 2019) and framed in SDS item format; *R* = reverse-worded item in SDS.

2.4. Procedure

Participants read an Explanatory Statement and completed a Consent Form, and asked any questions they had. After consent, participants completed a background questionnaire (age, sex) and the SDS. Participants were checked to see that they had refrained from caffeine or other substances that may influence their concentration and/or psychophysiological state in the 12 h prior to their EEG recording (all had followed this direction). Participants' scalps were then prepared and the electrode cap fitted; all electrode impedances were checked to ensure that they were < 5 kΩ. Participants were then taken to an experimental booth so that external stimuli were minimized, had headphones placed upon their ears to exclude extraneous noise and supply a pre-recorded transcript of all instructions to participants to ensure consistency. Participants were asked to relax. After 15 min of sitting still (adaptation), the audio-recorded experimental protocol for 3 min eyes closed was presented. Following the end of the protocol, participants left the experimental booth, had the headphones and electrode cap removed, and were thanked for their participation. Ethics approval for this study was provided by the Human Research Ethics Committee of the University of New England, Australia (Approval No. HE14–051).

2.5. Statistical analyses

Some initial data analyses were conducted to check scale internal consistency, normality, and differences between male and female, and depressed and non-depressed participants via ANOVA. Because the major focus of this study was upon the association between AA and Melancholia, data analysis followed the advice of Kołodziej et al., al. (2021) to apply correlation-based procedures to AA-depression data rather than ANOVA procedures that rely upon dichotomy (with its inherent limitations upon statistical outcomes: Cohen, 1983). Three separate sets of analyses were undertaken to measure the correlation between Melancholia and AA: for the entire sample, for the non-depressed participants, and for the depressed participants. As well as referring to the traditional level of significance of $p < 0.05$ as the indicator of results relatively free from Type I errors, results were also scrutinized according to the recommended method of identifying a meaningful outcome via effect size (APA, 2020), using Cohen's (1988) definition of a medium-strength correlation coefficient (i.e., $r = 0.3$ or

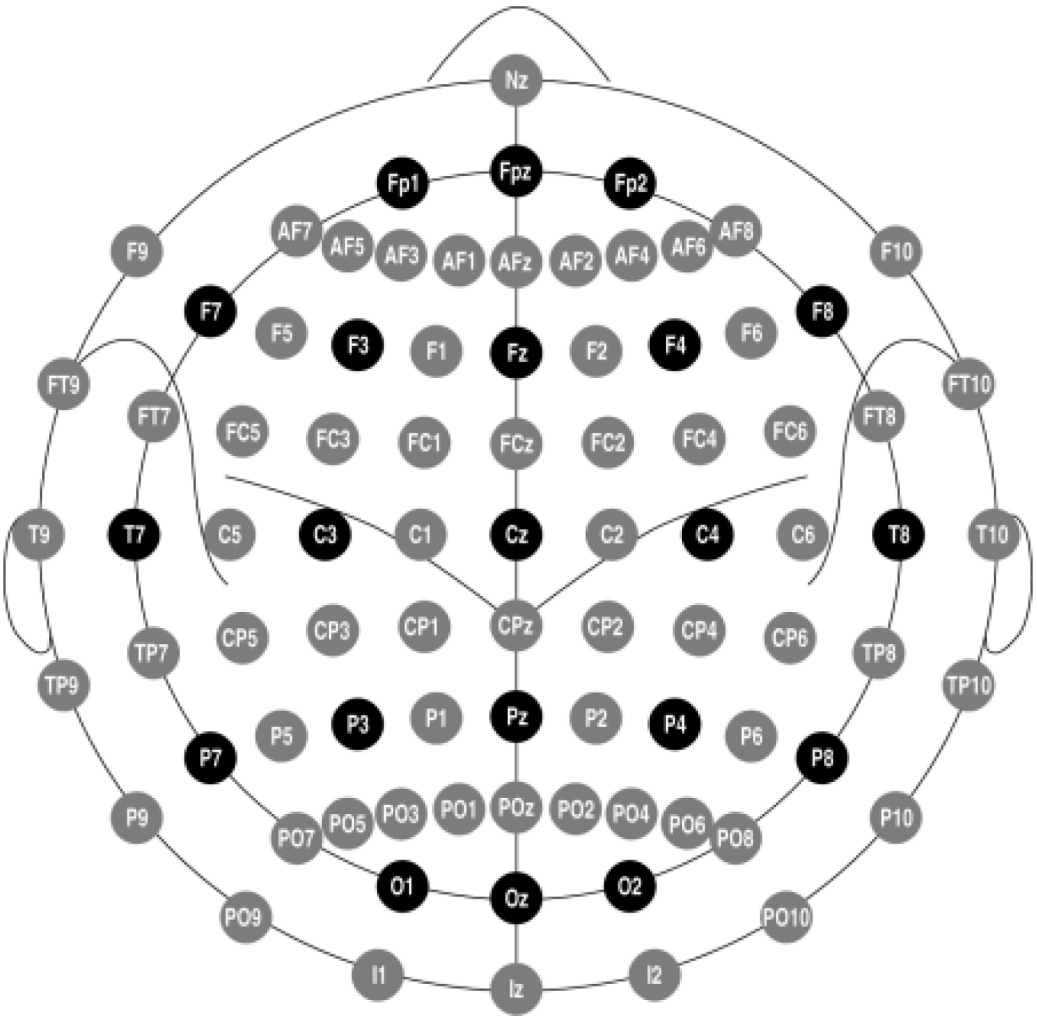

Fig. 1. Extended 10:20 EEG electrode sites, from Oostenveld and Praamstra (2001), Fig. 1.

greater). Although application of some form of correction to *p* values (e.g., Bonferroni) can be used to reduce the likelihood of a Type I error, this can also increase the likelihood of a Type II error, and there are arguments against such correction, particularly in exploratory studies such as this one (Rothman, 1990; Streiner and Norman, 2011); that position was adopted here.

3. Results

3.1. Data

The internal consistency (Cronbach alpha) for the SDS was 0.921, and for the 9-item Melancholia scale, it was 0.894. The normal Q-Q plots for the SDS and the Melancholia scale approached a straight line (indicative of a reasonably normal distribution), and the histograms were similar to normal, allowing the raw data from these scales to be used. As is traditional in the EEG field, raw EEG data were log transformed. The mean (SD) SDS and Melancholia score data for the entire sample, for the 33 participants who met Zung's criteria for clinically significant depression (i.e., SDS total score of at least 40), those 67 participants who did not meet that criterion, and for males and females, are shown in Table 2. As expected, MANOVA, using the Type II Sums of Squares, and referring to Pillai's Trace because of the difference in subsample sizes (Tabachnik and Fidell, 2013), revealed that the clinically significant depressed subsample had significantly higher SDS scores $F(1,99) = 257.645$, $p < 0.001$, $\mu^2 = 0.729$ than those participants who did not reach that level of SDS total score. This was also true for Melancholia scale total scores $F = 195.329$, $p < 0.001$, $\mu^2 = 0.670$. In addition, the clinically significantly depressed subsample had significantly higher scores on each item of the SDS, and each of the Melancholia scale items (all $p < 0.001$: see Fig. 2 for further detail of means and standard errors for the Melancholia scale) than the non-clinically significant participants. There were no significant differences between males and females on either the SDS $F = 0.023$, $p = 0.880$, or the Melancholia scale $F = 0.238$, $p = 0.626$, or on any of the two sets of individual items, allowing data from both sexes to be combined.

Table 2
Descriptive data for SDS[1] and Melancholia scale.

Sample	SDS *M* (SD)	Melancholia scale *M* (SD)
Total ($n = 100$)	36.700 (11.256)	15.180 (5.522)
Clinically significant depression ($n = 33$)	50.393 (7.432)	21.636 (3.912)
Non- clinically significant depression ($n = 67$)	29.955 (4.828)	12.000 (2.685)
Males ($n = 44$)	36.182 (10.309)	14.727 (5.336)
Females ($n = 56$)	37.107 (12.023)	15.535 (5.685)

[1]Zung self-rated depression scale.

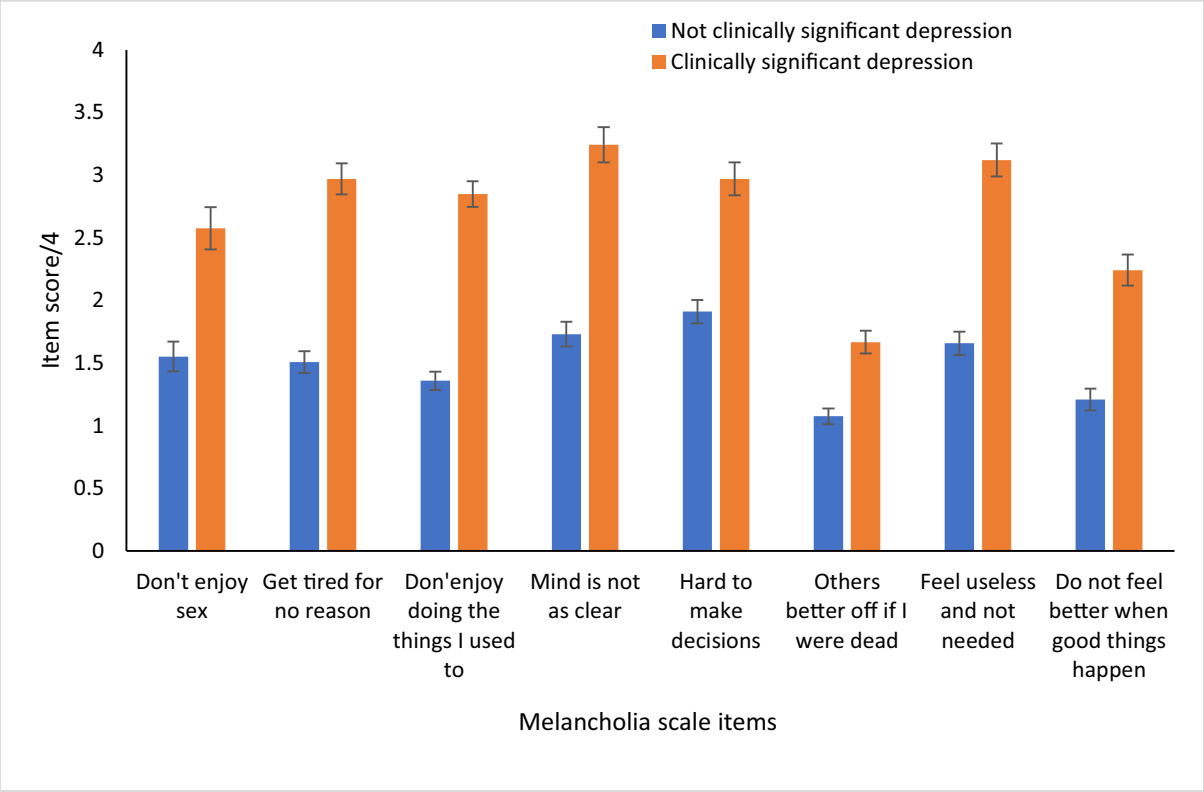

Fig. 2. Mean (Standard error) scores on Melancholia scale items (reverse wording removed) for 67 participants without clinically significant depression and 33 participants with clinically significant depression.

3.2. SDS, melancholia total score, and AA correlations

There were no significant correlations between any of the 12 sets of AA data and the SDS total score (all $r < 0.125$), or the Melancholia scale score (all $p > 0.175$) for the total sample, or for the non-clinically significantly depressed participants (SDS total score: all $p > 0.176$; Melancholia Scale score: all $p > 0.095$). There were no significant correlations between the AA data and the SDS for the clinically significant depressed participants (all $p > 0.090$), but there were significant correlations between these participants' Melancholia total scores and their AA data from FP2–FP1 (r = -0.388, p = 0.026), and from F4-F3 (r = -0.413, p = 0.017) (see Fig. 1 for location of these sites).

3.3. Melancholia symptoms, factors, and AA

Several significant correlations were found between specific items from the Melancholia Scale and AA data, shown in Table 3. In general, and consistent with some of the previous literature reviewed in Section 1.3, correlations between Melancholia items and AA were in the opposite directions for the frontal versus the parietal-occipital sites.

To explore possible reasons why there were significant correlations between AA data on only four of the eight items that comprised the Melancholia scale, factor analysis (FA) was performed on these data for the clinically significant depressed participants. Although the sample size was limited, the ratio of participants to items was over 4:1, judged as suitable by Cattell (1978), although this sample size requirement for FA has been robustly challenged by de Winter et al. (2009), with demonstrated reliable FA being conducted with samples as low as 10. Others have argued that the key issues with FA are the presence of many inter-item correlations of at least 0.3 (Tabachnik and Fidell, 2013), a Kaiser-Meyer-Olkin measure of sampling adequacy (Kaiser, 1970) of at least 0.6, and a significant Bartlett's test of sphericity (Bartlett, 1954); all three of these criteria were met here. By reference to eigenvalues > 1.0,

Table 3
Significant correlations between Melancholia scale symptoms and EEG AA1 data.

Melancholia symptoms[2]	Significant correlations AA site	r	p
Anhedonia (*Don't enjoy sex*)	FT8-FT7	−0.352	.044
Low energy (*Feel tired for no reason*)			
Loss of interest (*Don't enjoy doing things I used to*)			
Impaired concentration (*Mind is unclear*)			
Impaired concentration (*Hard to make decisions*)	F4-F3	−0.386	.027
	FC4-FC3	−0.371	.034
Thoughts of death/suicide (*Others better off if I was dead*)	PO2-PO1	.516	.003
Thoughts of death/suicide (*Feel useless and not needed*)	F4-F3	−0.377	.031
	PO2-PO1	.403	.027
Lack of improvement in mood (*Don't feel better when good things happen*)			

[1]Alpha wave asymmetry' [2] Reverse wording has been removed for clarity of content.

the scree plot, and confirmed by parallel analysis, the FA produced a simple two-factor solution, shown in Table 4, with interpretative titles for those factors.

Factor 1 *Fatigue-withdrawal* accounted for 33.928% of the variance, and Factor 2 *Social reasoning, misinterpretation* accounted for a further 17.161% of the variance; these factors were only moderately correlated (r = 0.369, p = 0.039), suggestive of orthogonality, and allowing either Varimax or Oblimin rotation; both of these procedures produced identical simple solutions. By comparison between Tables 3 and 4, it is apparent that only items from the Factor 2 *Social reasoning, misinterpretation* were significantly correlated with AA data. Fig. 3 more clearly depicts the ways that the four Factor 2 items were associated with the four EEG AA site data. Although only those correlation coefficients that

Table 4
Two factor solution for Melancholia scale1, showing symptoms and items.

Factor 1: Fatigue-withdrawal	Factor 2: Social reasoning, misinterpretation
	Anhedonia *(Don't enjoy sex)*
Low energy *(Feel tired for no reason)*	
Loss of interest *(Don't enjoy doing the things I used to)*	
Impaired concentration *(My mind is not as clear as it used to be)*	
	Impaired concentration (*I find it hard to make decisions)*
	Thoughts of death, suicide (*Others would be better off if I were dead)*
	Thoughts of death, suicide (*I feel useless and not needed)*
Lack of improvement in mood *(I don't feel better even when good things happen)*	

[1]Reverse wording removed.

reached statistical significance ($p < 0.05$) were included in Table 3, Fig. 3 highlights the presence of a larger number of correlation coefficients between the four Melancholia Factor 2 items and the four EEG sites' AA data in order to better portray the complete set of associations between these Melancholia symptoms and EEG AA data.

3.4. Melancholia factors and AA

It is apparent from Table 3 and Fig. 3 that the four symptoms comprising Melancholia Factor 2 *Social reasoning, misinterpretation* were differentially correlated with EEG AA sites. The items *I don't enjoy sex, I find it difficult to make decisions,* and *I feel useless and not needed* were inversely correlated with EEG AA from the frontal regions (FT8-FT7, F4-F3, FC4-FC3), but the item *Others would be better off if I were dead* was directly correlated with EEG AA in the parietal-occipital region (PO2-PO1). The item *I feel useless and not needed* was also directly correlated with EEG AA in the parietal-occipital region (PO2-PO1). On the basis of their different correlations with EEG sites, these four Melancholia Factor 2 *Social reasoning, misinterpretation* items were able to be further allocated into three subcomponents of that factor. These subcomponents were named Behavioural inhibition (*I don't enjoy sex, I find it hard to make decisions*) which was inversely correlated with frontal region AA; Negative self-evaluation (*Others would be better off if I were dead*), directly correlated with parietal-occipital region AA; and Social disconnect (*I feel useless and not needed*), directly correlated with the parietal-occipital region AA and also inversely correlated with frontal region AA. Each of these subcomponents was strongly correlated with the total score for Melancholia Factor 2 *Social reasoning, misinterpretation:* Subcomponent Behavioural inhibition $r = 0.864$, $p < 0.001$ (74.6% of the variance); Subcomponent Negative self-evaluation $r = 0.649$, $p < 0.001$ (42.1% of the variance); and Social disconnect $r = 0.625$, $p < 0.001$ (39.1% of the variance), but less strongly correlated with each other (both $r < 0.370$ (13.7% of the variance), suggesting that they represented moderately discrete aspects of Melancholia Factor 2 *Social reasoning, misinterpretation.*

3.5. Influence of depression severity

The significant correlations between Melancholia Factor 2 items and selected EEG AA site differences that are depicted in Table 3 and Fig. 3 are based upon the AA data, i.e., the difference between right- and left-brain hemisphere activity and the Melancholia scale items. Because of the influence of depression severity upon Melancholia that was reported by Parker et al. (1994; 2019), it is of interest to determine if the difference between the correlations for Melancholia score and EEG AA that was found for participants with clinically significant depression versus those without that severity of depression, was due to differences in: (i) Melancholia scale item scores (differences verified in Fig. 2); (ii) the EEG site alpha activity divorced from the AA calculation; or (iii) a combination of both of these effects. MANOVA (Type II Sums of Squares) on the alpha wave power for the eight EEG sites that comprised the four sets of AA data, for the clinically depressed vs non-clinically depressed participants, produced a nonsignificant main effect $F(8,76) = 0.615$, $p = 0.763$, $\mu^2 = 0.06$ (Pillai's Trace), and none of the univariate effects were significant. Therefore, because the difference in Melancholia scale item

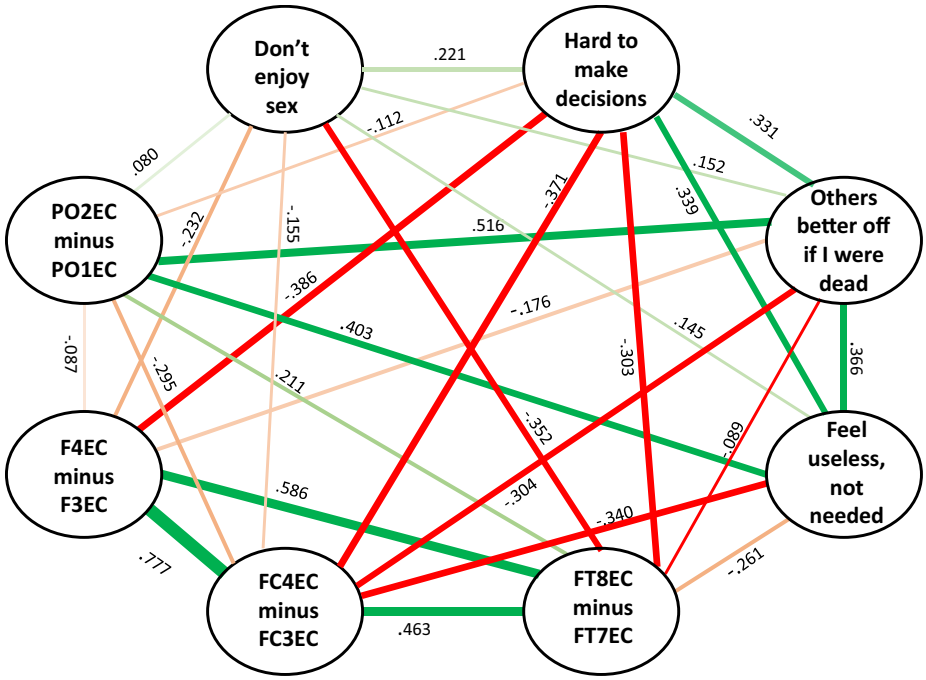

Fig. 3. Networks connecting Melancholia Factor 2 items and EEG AA sites, with correlation coefficients.
Note: EC = Eyes closed; PO = Parietal-occipital; *F* = Frontal; FT = Fronto-temporal; green lines = direct correlations; red lines = inverse correlations; strength of association is shown by width and shade of line.

scores was reported above (see Fig. 2), the suggestion made by Parker et al. (1994; 2019) that severity of depression was a major influence upon Melancholia was supported by these results, with relative EEG site alpha activity being an outcome of that difference in depression severity.

4. Discussion

4.1. Overall findings

The isolation of significant correlations between the Melancholia total score and AA data to only those participants who met Zung's (1973) criteria for clinically significant depression confirmed the influence of depression severity on Melancholia that was previously reported (Parker et al., 1994, 2019). Because those symptoms used to identify Melancholia are derived from the wider range of MDD symptoms, this is not unexpected on a statistical and content base, but it also explains the difficulty in clinically identifying patients who have Melancholia apart from those with simple severe global MDD, when that identification is performed purely upon their MDD symptoms. In that light, consideration of the associations between Melancholia symptoms and EEG AA data may provide a more reliable method of identifying Melancholic patients from global severe MDD patients.

4.2. Melancholia and AA

The significant associations between Melancholia total score and AA found in this study were confined to just two EEG sites (FP2-FP1, F4-F3). Of the limited number (i.e., 5) of previous studies of AA and Melancholia recently reviewed by Bruun et al. (2021), only one (Kano et al., 1992) identified specific EEG site activity that was significantly associated with Melancholia, namely increased beta activity in F4 and C4 sites. Therefore, the present findings are unique, and suggest that the association between total Melancholia score and AA in severely depressed participants is a function of frontal and parietal lobe activity differences from right to left side of the brain. Because the correlation found for Melancholia total score was inverse, and the Melancholia total score was positive, then the AA must be a negative value, which indicates greater alpha activity in the left side of the brain (i.e., FP1/F3) compared to the right side of the brain (i.e., FP2/F4). Conversely, because alpha reflects the relative absence of overall cortical activity in other frequencies (such as beta), then these results are indicative of greater cortical activity in the right side of the brain. This is congruent with previous reports of the association between depression and AA (Deslandes et al., 2008; Henriques and Davidson, 1990, 1991), and also agrees with the hypothesis that the behavioural inhibition system (BIS) (situated in the right frontal side of the brain) is dominant over the behavioural activation system (BAS) (situated in the left frontal side of the brain) (Alloy et al., 2008; McFarland et al., 2006) in depressed persons, because the BIS acts to withdraw the individual from aversive stimuli (Muscatell et al., 2009), and induces several of the key 'withdrawal' symptoms of MDD (Dougher and Hackbert, 1994; Ferster, 1973). It may be concluded from these results that the total Melancholia score used in this study was an outcome of the BIS over the BAS, as have been found for global depression. That finding is of interest, but does not allow understanding of those aspects of Melancholia that may have specific AA associations that are unique. Exploration of the factors of Melancholia provided a method for that further understanding of the nature of Melancholia,

4.3. Subcomponents of melancholia and AA

When examined at the individual Melancholia symptom level, total Melancholia score was found to be representative of two different aspects of Melancholia, as evidenced by the results of the Factor Analysis, and the associations between AA and the two Melancholia factors derived from the factor analysis. Although Melancholia Factor 1 *Fatigue-withdrawal* was not significantly associated with AA at any site, Melancholia Factor 2 *Social reasoning, misinterpretation* was, suggestive of two different subforms of Melancholia, only one of which had neurophysiological associations with alpha asymmetry. This subdivision of Melancholia on the basis of EEG data has not been previously reported.

The correlation coefficients between AA and the items that were included in the Melancholia factor 2 *Social reasoning, misinterpretation*, shown in Table 3, may be grouped into inverse and direct coefficients. The former include all the associations between Melancholia factor 2 *Social reasoning, misinterpretation* and frontal lobe regions, and are consistent with the results found for the total Melancholia score and the BIS > BAS hypothesis. By contrast, the remaining two items in Melancholia factor *Social reasoning, misinterpretation* were directly correlated with the difference between PO2 and PO1, which is in the parietal-occipital region. The direction of the correlation coefficient for these sites (i.e., the associations between Melancholia factor *Social reasoning, misinterpretation* and PO2-PO1 AA) were positive, and indicated that, unlike the frontal region findings, the left side of the parietal-occipital regions of the brain showed greater cortical activity than the right side. This has been previously reported for MDD patients classified dichotomously (Ma et al., 2016; Zhang et al., 2021), but not for the kind of detailed symptom-level analysis undertaken here, and suggests a differential model of electrical activity across brain regions for the *Social reasoning, misinterpretation* aspect of Melancholia.

4.4. The role of the parietal-occipital lobe

To better understand these findings, it is relevant to consider that the Parietal-Occipital region is linked with visuo-attentional networks which may contribute to deficiencies in attentional filtering of information, previously found in MDD patients (Desseilles et al., 2011). Capacity of visual working memory has been found to predict performance on a range of cognitive outcomes, particularly influenced by the functions of the intraparietal sulcus, which are thought to be linked with the individual's ability to control their personal representations of reality rather than their general attention (Gosseries et al., 2018). This explanation gives rise to the hypothesis that left hemisphere activation in the parietal-occipital region (and perhaps the intraparietal sulcus in particular) may contribute to the depressed individual being prone to misinterpreting real-world experiences in ways that make them believe that *Others would be better off if I were dead*, and *I am useless and not needed.* Following this argument, it may be plausible to subdivide Melancholia factor 2 *Social reasoning, misinterpretation* into two parts: one, which is characterized by *lack of enjoyment* in basic activities (sex) and an *inability to make decisions*, which is an outcome of the dominance of the BIS over the BAS, as the individual fails to engage with their social environment; and two, which is characterized by very poor self-belief (*death, suicide, uselessness, not needed*), initiated by unrealistic visual working memory of social interactions and resultant misinterpretation of those interactions to the point where the individual believes that they are unwanted and useless. The finding that the Melancholia factor 2 symptom *I feel useless and not needed* was significantly correlated with both frontal AA (inversely, for the F4-F3 site alpha wave differences) and also with parietal-occipital AA (directly) suggests that this particular symptom (which occurs in both MDD and Melancholia) may be influenced by the BIS>BAS dominance and also the individual's difficulties in perceiving real-world experiences accurately. This anterior-posterior difference in AA has been previously described by Heller and Nitscke (1997), but has been only partially confirmed by previous studies of MDD participants (Mennella et al., 2015), perhaps because of the influence of melancholic participants within the overall MDD sample.

This explanation of the association between EEG AA and Melancholia data is hypothetical at this stage, and requires replication before it can be accepted. However, previous studies of Melancholia and AA have been limited because they considered Melancholia solely from a global score perspective. As suggested above, Melancholia (like MDD) appears

to be heterogeneous, and these findings provide some initial evidence for considering this aspect of depression in the same way as is recommended for MDD itself (Chekroud et al., 2017; Ostergaard et al., 2011).

As a final note in this initial explanation of the findings reported here, in terms of the relevant EEG AA sites found to be significantly associated with Melancholia factors and subcomponents, Fig. 3 indicates robust direct correlations between the three sets of AA data collected from the frontal sites, but only weak direct or inverse correlations between each of those three sets of frontal EEG AA data and the parietal-occipital AA data. This suggests that the differential correlations found between the Melancholia factor 2 *Social reasoning, misinterpretation* subcomponents and EEG AA data were an outcome of the different cognitive processes thought to occur in the frontal versus parietal-occipital regions as well as the content of the four Melancholia scale items shown in Fig. 3. Of those four Melancholia items, three were intercorrelated at moderate strength level (Cohen, 1988), but one, the single anhedonia item *I don't enjoy sex*, was only weakly correlated with each of the remaining three Melancholia items. Further, that single anhedonia item was statistically significantly correlated with only one of the four EEG AA sites (i.e., FT8-FT7). Taken together, these results suggest that sexual anhedonia may represent a relatively different aspect of Melancholia than symptoms about the participant's ability to think positively about themselves. There is no obvious generalization from these results about a single target of anhedonia (i.e., sexual activity) and any other hedonic-inherent activities or stimuli, and these results urge further investigation of this aspect of Melancholia and its neurophysiological associations.

4.5. Limitations

Limitations of this study include the size of the sample; replication of this study with larger samples, drawn from different social and geopolitical locations, would allow for stronger generalizability. Many studies have used a dichotomous diagnostic system for MDD or Melancholia, but the limitations of that process have been explicated earlier in this paper. By contrast, the use of a multi-symptom scale enabled a more detailed investigation of both depression overall and also the construct of Melancholia. However, clinician diagnosis can provide a valuable alternative index of depression and its subtypes, and so triangulation of the clinician diagnosis and multi-symptom self-report could be a valuable addition to future studies. The data reported here were from a cross-sectional study, and conclusions suffer from a lack of information regarding fluctuations over time and circumstance. EEG data provide a unique perspective on brain activity, but combinatory data from other imaging procedures such as fMRI could build a more detailed picture of the underlying brain activity that is associated with Melancholia and its components. In terms of the study's major strengths, the measurement of Melancholia was based upon a series of thoughtful studies (particularly Parker et al., 1994, 2019), and was of greater validity than some previous methods that used a clinician's interpretation of various DSM-based nomenclature. Although the sample was limited in size, it was reasonable compared to previous studies, and found to be satisfactory for the statistical procedures used via *a priori* power analysis.

4.6. Conclusions

Notwithstanding these limitations, the findings from this study present an adequately powered and detailed analysis of the association between Melancholia and brain activity. By demonstrating the association between the total score on a well-validated multi-symptom Melancholia scale and specific EEG AA, the previous literature was extended. The major contribution of this study was its examination of the structure of Melancholia, and the demonstration that there were differences in the EEG AA associations between the two Melancholia factors, plus an initial argument that the factor which was significantly associated with EEG AA might also be subdivided on the basis of the specific symptoms and their link with particular brain sites and functions.

Data availability

Data are available from the first author on reasonable request.

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Ethical approval

Approved by Human Research Ethics Committee of the University of New England, Australia (Approval No. HE14–051).

All participants gave written consent.

Declaration of Competing Interest

None of the authors has any conflict of interest to declare.

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