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Research paper

Altered activity in functional brain networks involved in lexical decision making in bipolar disorder: An fMRI case-control study

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ABSTRACT

Background: Brain networks involved in language, attentional and response processes are detectable by fMRI during lexical decision (LD). Here, we investigated possible abnormalities in the functional networks involved in LD in patients with bipolar disorder (BD).

Methods: fMRI and behavioural data were compared between BD (n = 25) and control (n = 21), with groups matched for age and sex. The functional brain networks involved in LD were extracted by manipulating the "word-likeness" of LD stimuli and using a multidimensional analysis method.

Results: Attentional, response and language processes were captured in separate function-specific brain networks (default mode network, response network, linguistic processing network, respectively) in the BD and control groups, replicating the results of our previous study in an independent group of healthy adults. Behaviourally, the BD group showed higher performance than the control group in the LD task. Activity in the default mode network (DMN) and the linguistic processing network (LPN) did not differ between the groups, but the BD group had higher activation than the control group in the response network (RESP).

Limitations: Due to the small sample, the study is underpowered, capable of only detecting large effects.

Conclusions: The results suggest that BD may be associated with sustained activity in the RESP network, which might contribute to psychomotor dysfunction in BD. Future studies should investigate the possible link between altered RESP activation and psychomotor disturbances in BD, as well as the basis for altered RESP activity in BD.

1. Introduction

Deficits in neuropsychological function are key features of bipolar disorder (BD). These impairments include deficits in attention, language and psychomotor function (Bora et al., 2009; Cullen et al., 2016; Raucher-Chéné et al., 2017). Attentional deficits have been shown to be present in the manic and depressive states of BD (Najt et al., 2005) and to persist during the euthymic state of the disorder (Ancín et al., 2010). Disturbances in language and psychomotor functioning are thought to be state-dependent in BD (Magioncalda et al., 2020; Weiner et al., 2019). That is, bipolar patients in the depressive state have been observed to exhibit a paucity in content of speech, while those in the manic state tend to have pressured speech and flight of ideas via punning or rhyming associations (Weiner et al., 2019). Bipolar depression has also been associated with psychomotor inhibition, while bipolar mania has been linked with psychomotor excitation (Magioncalda et al., 2020).

The brain networks involved in language, attentional and motor response processes can be detected by fMRI during lexical decision (LD) task performance (Murphy et al., 2019; Wong et al., 2020). The LD task typically involves the presentation of a list of words or non-word foils. Subjects performing the LD task are required to indicate whether the presented item is a real word or not. The LD task has been used to investigate linguistic processing in several clinical populations, including schizophrenia (Natsubori et al., 2014) and dementia (Nikolaev

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et al., 2019). However, to our knowledge, no previous study has tested the LD task in BD patients.

As attentional and response processes are elicited along with access to lexical representations during LD, these processes can be confounded in fMRI studies of LD. We previously published an fMRI study in which we manipulated the "word-likeness" of LD stimuli to facilitate the separation of attentional demand and response processes from linguistic processing in healthy adult participants (Wong et al., 2020). The task consisted of word and non-word stimuli taken from the English Lexicon Project database (Balota et al., 2002) at two levels of difficulty ("regular" or "hard"); this created four experimental conditions: regular word (e.g., beef), regular non-word (e.g., ralc), hard (obscure) word (e.g., rein), and hard (word-like) non-word (e.g., sone). Using "word-like" non-words as foils in the LD task makes it harder to distinguish words from non-words by means of orthographic, phonemic and semantic information (Ratcliff et al., 2004). Hence, correctly rejecting hard (word-like) non-words requires the suppression of lexical representations that are carried with these foils. By contrast, obscure words require increased linguistic resources to facilitate correct identification as real words (Ratcliff et al., 2004; Wong et al., 2020). Therefore, a functional network underlying access to lexical representations should show increased activity for the hard (obscure) word condition and decreased activity for the hard (word-like) non-word condition. In contrast, attentional networks are expected to be sensitive to task difficulty regardless of lexical content, and thus are expected to respond intensely to both the hard word and non-word conditions, compared to the regular word and non-word conditions. Response networks are expected to not be sensitive to lexicality or difficulty; hence, activity in response networks should be similar between the conditions.

By manipulating the word-likeness of LD stimuli along with a multidimensional analysis method, we extracted three functional brain networks involved in the LD task in our previous study in healthy adults (Wong et al., 2020). One of these networks involved default mode network (DMN) regions, which showed increased deactivation as attentional demand increased. DMN deactivation was most pronounced in the hard non-word condition, which was associated with the slowest RT, suggesting that it was the most difficult condition (Wong et al., 2020). Component 2 consisted of motor response network regions and areas associated with visual attention. This network showed more sustained activation for the hard condition than the regular condition, likely reflecting the slower RTs in the hard condition, but showed no differences between the word and non-word conditions. The lack of sensitivity to lexicality is in accordance with the postulation that this network is mainly involved in motor response processes, hence it was referred to as the response network (RESP; Wong et al., 2020). Component 3 comprised brain regions involved in linguistic processing, with activations in left prefrontal regions and left middle temporal gyrus. This linguistic processing network (LPN) showed the highest activation for the hard word condition, indicating its involvement in accessing lexical representations, and the *lowest activation for the hard (word-like) non-word condition*, suggesting that reduced activation of this language network was required to avoid false positives when the non-word stimuli were more word-like (Wong et al., 2020).

The aim of the current study was to investigate LD task performance and the functional networks involved in LD in BD patients. The BD group was compared to a community control group to assess for possible LD abnormalities in BD. We manipulated the "word-likeness" of LD stimuli combined with a multidimensional analysis method to extract the functional networks involved in LD. We hypothesized that our previous LD results in healthy participants (Wong et al., 2020) would be replicated in a new sample of BD patients and controls with respect to extraction of networks (i.e., LPN, DMN and RESP) and the patterns of associated hemodynamic responses as was detailed above for attention vs. linguistic vs. response processes. As BD has been associated with impaired attention, language, and psychomotor function, we hypothesized that the BD patients would show impaired LD task performance compared to controls. We also hypothesized that the patients would show altered activations in the functional networks associated with LD.

2. Methods

2.1. Participants

Twenty-six patients with BD and 25 community control participants took part in the study. One BD patient and four control participants were excluded due to data acquisition issues, leaving a final sample size of 25 BD patients (23 BD type I and 2 BD type II) and 21 community control participants. Five of the BD patients met current criteria for a depressive episode, four met criteria for a manic episode, and one met criteria for a hypomanic episode. Our final sample size of 25 BD patients and 21 control participants has a power of 0.76 in a repeated measures ANOVA with $\alpha = 0.05$ and effect size of $d = 0.4$ (R version 4.2.0).

The BD patients were recruited through an outpatient mood disorder clinic, through the Organization for Bipolar Affective Disorder Society in Calgary, Alberta, and online and community advertisements. The controls were recruited from the community using advertisements. All participants were screened using the following exclusion criteria: 1) age <18 or >60; 2) diagnosis of a substance-related disorder in the last three months (excluding nicotine, caffeine and cannabis); 3) use of inhalants three or more times; 4) history of head injury with loss of consciousness for >30 min; and 5) a history of electroconvulsive therapy, epilepsy, seizures, diabetes, legal blindness, stroke, MRI contraindications, or any medical or neurological condition that would make it impossible to complete the study. Controls were also excluded from the study if they had a history of major depressive disorder, had used antipsychotic or antidepressant medication, or had a personal or family history of a psychotic or bipolar related disorder. Written consent was obtained from all participants. The study obtained ethics approval from the University of Calgary's Conjoint Health Research Ethics Board (CHREB).

2.2. Clinical and cognitive assessments

Diagnosis of mood, psychotic, substance use, and/or anxiety disorder was determined using the Structural Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders – 5th Edition (SCID-5; First et al., 2015). The Young Mania Rating Scale (YMRS; Young et al., 1978) and the Hamilton Depression Rating Scale (HAM-D; Williams, 1988) were used to evaluate recent symptoms of mania and depression, respectively. Functional ability was evaluated using the Functioning Assessment Short Test (FAST; Rosa et al., 2007) and the Social and Occupational Functioning Assessment Scale (SOFAS; Rybarczyk, 2011). The Wechsler Test of Adult Reading (WTAR; Wechsler, 2001) was used to estimate intelligence.

2.3. Lexical decision task

The LD task involved participants deciding whether four-letter sequences were real English words or not through right-handed button-press during fMRI scanning. All participants were instructed to respond 'yes' with index finger and 'no' with middle finger via a scanner compatible two-button response box. Instructions were displayed in the scanner before the beginning of the session. Once the participants finished reading the instructions, a button press prompted the onset of the scanning session as the task began. Word and non-word stimuli were selected from the English Lexicon Project database (Balota et al., 2002) at two levels of difficulty according to LD accuracy, with both being restricted to four letters. The "regular" level was characterized by an average of 96 % word and 97 % non-word categorization accuracy, and the "hard" level was characterized by an average of 86 % word and non-word categorization accuracy, as determined by the English Lexicon Project database. This produced four categories of stimuli to create four experimental conditions – regular non-word, hard (word-like) non-

Table 1
Reaction time (RT) and accuracy as a function of difficulty and lexicality and group status.

Condition		Description	Item	Reaction time (ms) Mean (SD)	Accuracy (%) Mean (SD)
Difficulty	Lexicality				
Control					
Hard	Non-word	Word-like non-word	Sone	1001 (153)	84 (18)
Hard	Word	Obscure word	Rein	928 (148)	87 (15)
Regular	Non-word	Regular non-word	Ralc	955 (219)	92 (12)
Regular	Word	Regular word	Beef	790 (148)	97 (4)
Bipolar					
Hard	Non-word	Word-like non-word	Sone	997 (141)	89 (12)
Hard	Word	Obscure word	Rein	884 (142)	94 (6)
Regular	Non-word	Regular non-word	Ralc	914 (136)	95 (7)
Regular	Word	Regular word	Beef	762 (90)	98 (3)

word, regular word, and hard (obscure) word (see Table 1 for examples). Each LD run consisted of six blocks of stimuli, which included three regular and three hard blocks. Each block consisted of 30 trials with equal number of word and non-word trials presented in random order. Block order and items within each block were randomized separately for each participant. A fixation period of 15 s was included at the beginning of each block. One second of fixation was presented before each trial, followed by 2 s of stimulus presentation, during which time participants categorized the stimulus as a word or non-word via button-press (see Fig. 1). Response time was recorded, but the stimulus remained on the screen for the full 2 s.

2.4. Image acquisition

Whole-brain images were collected at the Seaman Family Magnetic Resonance Research Centre at the University of Calgary on a 3 T General Electric Discovery MR750 system using an 8-channel head coil. fMRI data were collected through echoplanar imaging (EPI; TR/TE = 2500/30 ms, flip angle 77°, 40 slices, 3.4 mm thick, 0 mm slice spacing, 64 × 64 matrix reconstructed at 128, FOV = 22 mm) and 258 volumes. T2-weighted high-resolution scans were also acquired for each participant as structural scans for registering functional images to standard space (40 slices, 3.4 mm thick, TR/TE = 7500/120 ms, FOV = 22 mm, and matrix = 256 × 256).

Functional scans were reoriented to set the origin at the anterior commissure and the scan series were co-registered, normalized and realigned using the method implemented in Statistical Parametric Mapping 8 (SPM8; http://www.fil.ion.ucl.ac.uk/spm). Translation and rotation corrections for head movement did not exceed 3 mm or 3° for any of the participants. All images were normalized by first warping high-resolution structural images to a template of Montreal Neurological Institute (MNI) coordinate space, then applying these transformation parameters to the realigned functional images. Voxels were normalized to 2 × 2 × 2 mm. The normalized functional images were smoothed with

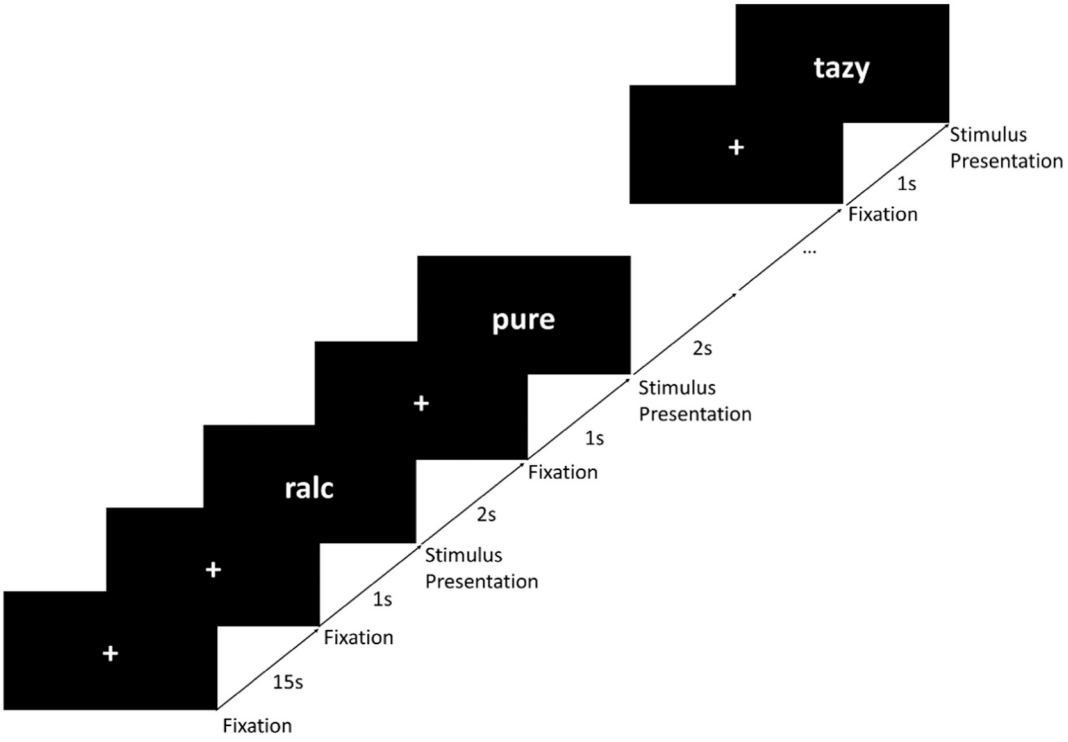

Fig. 1. Timeline of one block of stimulus presentations in the lexical decision (LD) task. After participants finished reading the instructions, 15 s of fixation was presented at the beginning of each block. One second of fixation was presented before each trial, followed by 2 s of stimulus presentation, during which participants respond via button press to four-letter sequences with index finger for "yes" (stimulus is a real English word), or with the middle finger for a "no" (not a real English word). One block consisted of 30 trials with equal number of word and non-word stimuli. Three "regular" blocks and three "hard" blocks were presented to each participant.

Table 2
Participant characteristics.

	Bipolar (n = 25)	Control (n = 21)	Test statistics
Age (years): mean (SD)	38.16 (11.11)	35.48 (7.82)	$t(44) = 0.93$, $p = .36$
Education (years completed): mean (SD)	14.43 (2.74)	15.86 (2.06)	$t(42) = -1.93$, $p = .06$
Sex (% female)	72.0	71.4	$\chi^2(1) = 0.002$, $p = .97$
Native language (% English)	96.0	66.7	$\chi^2(1) = 6.83$, $p = .009$
Occupation (% working or in school)	64.0	76.2	$\chi^2(1) = 0.80$, $p = .37$
Marital status (% married, never divorced)	19.6	23.9	$\chi^2(4) = 7.24$, $p = .12$
Handedness (% right-handed)	96.0	90.5	$\chi^2(2) = 1.24$, $p = .54$
WTAR standard score: mean (SD)	111.32 (11.86)	104.57 (25.39)	$t(41) = 1.12$, $p = .27$
YMRS: range (0–60)	0–16	0–4	
YMRS: mean (SD)	3.78 (3.75)	0.86 (1.24)	$t(27.12) = 3.53$, $p = .001$
HAM-D: range (0–52)	0–23	0–6	
HAM-D: mean (SD)	7.61 (6.87)	0.81 (1.40)	$t(24) = 4.64$, $p < .001$
FAST: range (0–72)	0–37	0–5	
FAST: mean (SD)	12.52 (9.40)	0.85 (1.42)	$t(23.16) = 5.88$, $p < .001$
SOFAS: range (0–100)	0–40	0–100	
SOFAS: mean (SD)	69.74 (13.07)	81.56 (22.41)	$t(23.23) = -1.86$, $p = .07$
Atypical antipsychotics (% on)	58.3	0	–
Typical antipsychotics (% on)	4.0	0	–
Anti-convulsants (% on)	56.0	0	–
Anti-depressants (% on)	33.3	0	–
Lithium (% on)	28.0	0	–
Sedative-hypnotics (% on)	8.0	0	–
Other psychiatric medications (% on)	4.2	5.0[a]	–

WTAR, Wechsler Test of Adult Reading; YMRS, Young Mania Rating Scale; HAM-D, Hamilton Depression Rating Scale; FAST, Functioning Assessment Short Test; SOFAS, Social and Occupational Functioning Assessment Scale.

[a] One participant in the control group was on lisdexamfetamine which is typically used for the treatment of attention deficit hyperactivity disorder (ADHD); this participant's SCID-5 scores did not show presence of a psychiatric disorder.

a Gaussian kernel (6 mm FWHM). All X Y Z coordinates listed in this manuscript are MNI coordinates.

2.5. Data analysis

2.5.1. Behavioural analysis

Condition-dependent effects in accuracy and RT were tested using a 2 × 2 × 2 repeated measures analysis of variance (ANOVA), with difficulty (regular vs. hard) and lexicality (word vs. non-word) as within-subject variables and group (BD vs. control) as a between-subject variable. To test for effects of demographic variables, accuracy and RT were each correlated with age and years of education, and the effect of sex was tested by adding a between-groups factor to the repeated measures ANOVA.

2.5.2. fMRI-CPCA

fMRI data were analyzed using constrained principal component analysis for fMRI (fMRI-CPCA; www.nitrc.org/projects/fmricpca) with orthogonal rotation (Lavigne et al., 2020; Metzak et al., 2011; Woodward et al., 2013). Conceptually, fMRI-CPCA is a combination of multiple regression analysis and principal component analysis (PCA; Takane and Hunter, 2001; Takane and Shibayama, 1991). Multiple regression is used to separate task-timing-predictable variance in the BOLD signal from task-unrelated variance, and PCA is applied to the task-related variance. Dominant sets of voxel-based component loadings are then interpreted spatially, alongside statistical assessment of temporal information in the estimated hemodynamic response (HDR) shape. The HDR is estimated by the predictor weights that result from regressing the component scores derived from the PCA back onto the task-timing based FIR model. The FIR model captures BOLD signal changes that are consistent over trials and occurring approximately 20 s after stimulus presentation. Thus, due to the nature of the FIR model, through fMRI-CPCA, we can (1) identify multiple functional networks that are simultaneously involved in a cognitive task, (2) estimate HDR shape occurring approximately 20 s following stimulus presentation for each network separately, for each participant and condition, and (3) statistically test the effect of task conditions on estimated HDR shapes for each network using ANOVAs.

2.5.3. Mixed-design ANOVA on predictor weights

As mentioned above, the HDR shape for each network is estimated by predictor weights for each component, with one value produced for each of the 8 post-stimulus time points, each of the 4 conditions, and each of the participants in the two groups. To statistically test for differences between conditions and groups, these are submitted to an ANOVA for each of the components. Thus, 8 × 2 × 2 × 2 mixed-design ANOVAs were carried out for each component, with post-stimulus time (8 TRs or full-brain scans), lexicality (word vs. non-word), and difficulty (regular vs. hard) as within-subject factors, and group (BD vs. control) as a between-subject factor. Interactions were interpreted by follow-up analyses involving simpler effects (i.e., sets of 2 × 2 interactions involving adjacent time points). The Shapiro-Wilk tests of normality were carried out for each time bin, across groups and conditions (total of 32 time bins for each group per component). Normality was present in all time bins, with the exception of one time bin in Component 1 for the control group, one time bin in Component 3 for the BD group, and two time bins in Component 3 (across two conditions) for the control group ($p < .01$). Tests of sphericity were carried out and Greenhouse-Geisser adjusted degrees of freedom were checked. Unadjusted degrees of freedom are reported, but only for effects that were also significant when adjusted degrees of freedom were used.

As explained above, predictor weights and their associated HDR shapes provide measures of individual differences. This allows for computation of relationships between functional networks computed over individual differences. HDR increases to peak (ITP) and returns to baseline (RTB) can be computed separately for each network because they are thought to index distinct cognitive processes (Lavigne et al., 2016; Woodward et al., 2013). To correct for the number of tests performed, we applied a threshold of $p < .01$ for statistical significance to reach a compromise between Type I and Type II errors. These computed ITP and RTB scores were then intercorrelated to study positive and negative interactions within and between functional networks. Statistical tests for differences between correlation coefficients (Raghunathan et al., 1996) were used to test for task-condition differences between these relationships with ITP and RTB, and their association with behavioural measures. To test for effects of demographic variables, ITP and RTB values were correlated with age and years of education. The

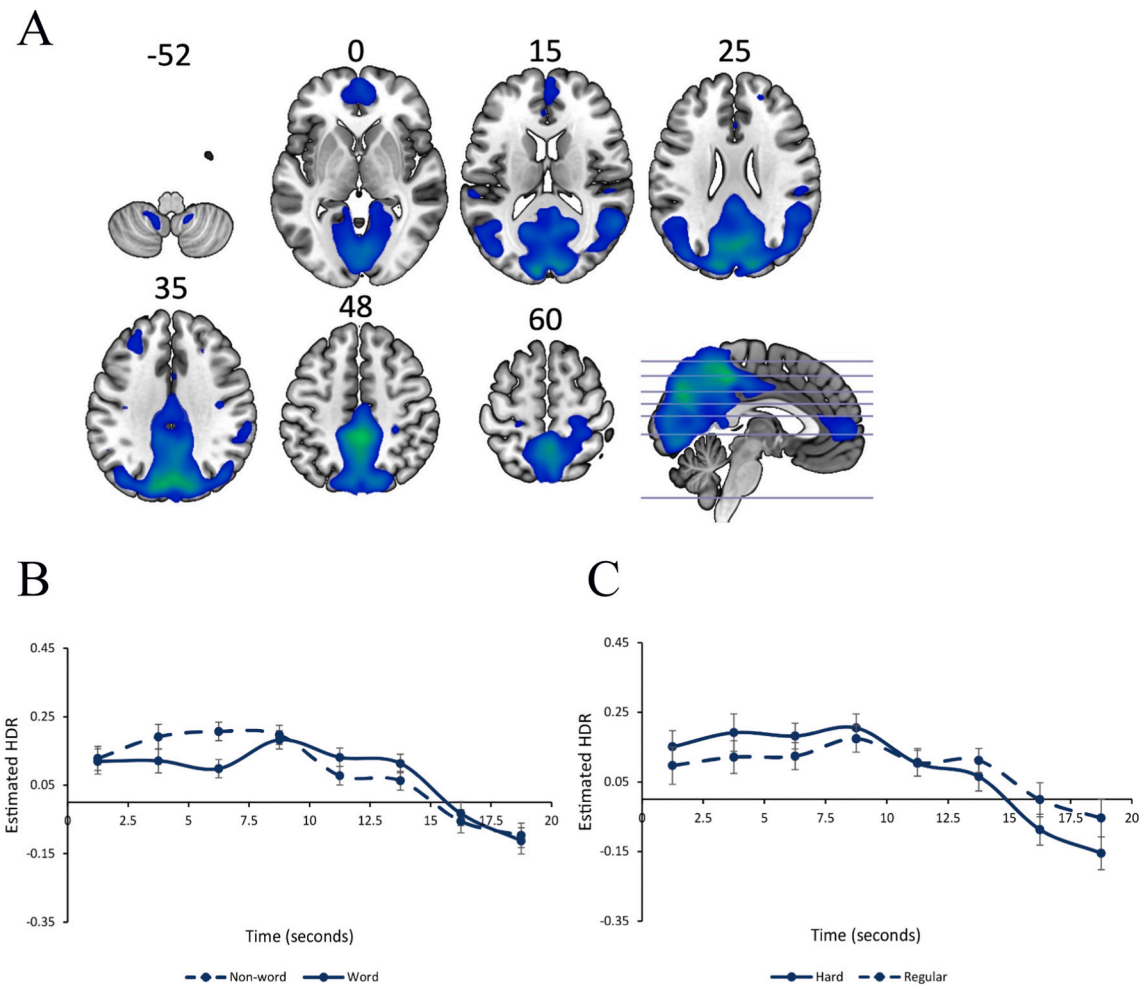

Fig. 2. A (top): Dominant 10 % of component loadings for Component 1, default mode network (DMN). Montreal Neurological Institute Z-axis coordinates are displayed. Images are displayed in neurological convention (left is left). Blue/green = negative loadings (threshold = −0.21, min = −0.38). B and C (bottom): mean finite impulse response (FIR)-based predictor weights by lexicality (B) and difficulty (C) of items, plotted as a function of post-stimulus time (TR = 2500 ms) and condition (averaged over group; error bars are standard errors). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

effect of sex was tested by adding a between-group variable to the mixed-design ANOVAs.

3. Results

3.1. Participant characteristics

Table 2 shows the participants' characteristics. Nonsignificant differences were found between BD and control groups for age, education, sex, handedness, and estimated intelligence. The proportion of native English speakers was significantly higher in the BD than the control group. As expected, significant group differences were found for YMRS and HAM-D scores with the BD group having higher (worse) scores on these measures. Function ability (measured using FAST and SOFAS) was lower in BD than the control group, although the difference in the SOFAS scores was not statistically significant.

3.2. Behavioural results

3.2.1. Accuracy

The means and standard deviations of the accuracy for both groups are shown in Table 1. The main effects of difficulty and lexicality were highly significant (both *ps* < .001). There was no main effect of group, $F(1,44) = 2.58$, $p = .12$. The interaction between group and lexicality was not significant, $F(1,44) = 0.05$, $p = .82$. However, there was a significant group × difficulty interaction, $F(1,44) = 4.73$, $p < .05$, $\eta^2 = 0.10$. This interaction was caused by a greater decrease in accuracy in the hard condition relative to the regular condition for the control group (95 % to 85 %) relative to the bipolar patients (96 % to 92 %). The difficulty × lexicality interaction was not significant, $F(1,44) = 0.21$, $p = .65$.

3.2.2. Response time

Table 1 shows the means and standard deviations of the RT for each group. The main effect of group was not significant, $F(1,44) = 0.58$, $p = .45$. Group × difficulty, group × lexicality, and group × difficulty × lexicality interactions were also not significant (all *ps* > .05). As such, the following RT effects were averaged over group. The main effects of difficulty and lexicality were significant (both *ps* < .001). A significant difficulty × lexicality interaction also emerged, $F(1,44) = 18.45$, $p < .001$, $\eta^2 = 0.30$. This was due to a significant contrast between all four conditions. Namely, slower RT of non-word versus word conditions in both regular, $F(1,44) = 78.00$, $p < .001$, $\eta^2 = 0.64$, and hard, $F(1,44) = 26.77$, $p < .001$, $\eta^2 = 0.38$, conditions as well as slower RT for hard versus regular conditions in both non-word, $F(1,44) = 29.61$, $p < .001$, $\eta^2 = 0.40$, and word, $F(1,44) = 124.94$, $p < .001$, $\eta^2 = 0.74$, conditions.

3.2.3. Correlation with demographic variables

Neither RT nor accuracy correlated with age or years of education.

Table 3
Cluster volumes for the most extreme 10 % of Component 1 loadings (DMN), with anatomical labels, Brodmann's areas, and MNI coordinates for the peak of each sub-cluster. Clusters smaller than 270 mm^3 were omitted.

Anatomical label	Cluster volume (mm^3)	Brodmann's area for peak locations	MNI coordinate for peak locations		
			x	y	z
Negative loadings					
Cluster 1: Bilateral	201,888				
Cingulate gyrus, anterior division		24	2	6	37
Precentral gyrus		6	26	−26	65
Supramarginal gyrus, anterior division		40	62	−34	33
Postcentral gyrus		3	28	−36	55
Precuneous cortex		23	2	−42	49
Cingulate gyrus, posterior division		26	−2	−42	27
Lingual gyrus		27	18	−42	−3
Cingulate gyrus, posterior division		27	10	−44	5
Lingual gyrus		37	28	−44	−9
Cingulate gyrus, posterior division		29	−8	−46	7
Lingual gyrus		37	−24	−46	−9
Cingulate gyrus, posterior division		30	6	−48	19
Angular gyrus		22	48	−50	23
Angular gyrus		21	56	−54	15
Precuneous cortex		17	14	−56	11
Angular gyrus		39	−46	−56	19
Precuneous cortex		17	20	−58	15
Lingual gyrus		19	−18	−60	−9
Intracalcarine cortex		17	−4	−64	9
Lingual gyrus		18	18	−70	−9
Lingual gyrus		18	14	−72	−7
Lateral occipital cortex, superior division		39	44	−72	29
Cuneal cortex		18	2	−74	31
Lateral occipital cortex, superior division		19	−44	−76	15
Precuneous cortex		7	6	−78	39
Lingual gyrus		17	6	−78	−5
Lateral occipital cortex, superior division		39	−38	−78	31
Cuneal cortex		19	−8	−80	39
Lingual gyrus		17	0	−84	−5
Occipital pole		18	−12	−88	29
Occipital pole		18	12	−90	21
Occipital pole		18	−8	−94	15
Occipital pole		18	6	−96	27
Cluster 2: bilateral	8760				
Frontal pole		10	2	56	5
Paracingulate gyrus		10	−10	50	1
Cingulate gyrus, anterior division		32	−4	40	9
Cingulate gyrus, anterior division		24	−2	32	17
Cluster 3: Left hemisphere	2056				
Frontal pole		46	−28	40	33
Middle frontal gyrus		9	−28	30	39
Cluster 4: Left hemisphere	984				
Cerebellum IX		n/a	−14	−50	−49
Cluster 5: Right hemisphere	680				
Precentral gyrus		6	48	−10	45
Precentral gyrus		3	38	−14	39
Cluster 6: Right hemisphere	384				
Frontal pole		46	22	48	27
Cluster 7: Left hemisphere	320				
Planum temporale		42	−60	−30	15
Cluster 8: Right hemisphere	296				
Cerebellum IX		n/a	14	−50	−51

Including sex as a between-groups factor in the 2 × 2 × 2 ANOVA did not produce any significant effects (all *ps* > .05).

3.3. Neuroimaging

A scree plot indexing the percentage of variance in the task-related brain activity of each of the rotated components indicated that three components should be extracted. Components 1–3 accounted for 10.49 %, 8.88 % and 5.42 % of variance in the task-related BOLD activity, respectively. The mixed-design ANOVAs for each component showed no significant four-way interactions (all *ps* > .05). Hence, only three-way interactions and simpler effects are reported.

3.3.1. Component 1: default mode network

The brain regions associated with Component 1 are displayed in Fig. 2A. Table 3 shows the anatomical description of the component. Supplementary Table S1 shows the correspondence of activity peaks in Component 1 with anatomical descriptions, Brodmann's areas (BAs) and resting state networks. Slice comparisons between the current study and previous studies (Metzak et al., 2012; Wong et al., 2020) in our lab for Component 1 are shown in Supplementary Fig. S1. The regions deactivating (negative loadings set in blue/green in Fig. 2A) in this component corresponded with DMN regions (Buckner et al., 2008); this included the precuneus (BA 17), frontal pole (BA 46) and angular gyrus (BA 39).

A significant main effect of group was not observed for activation in

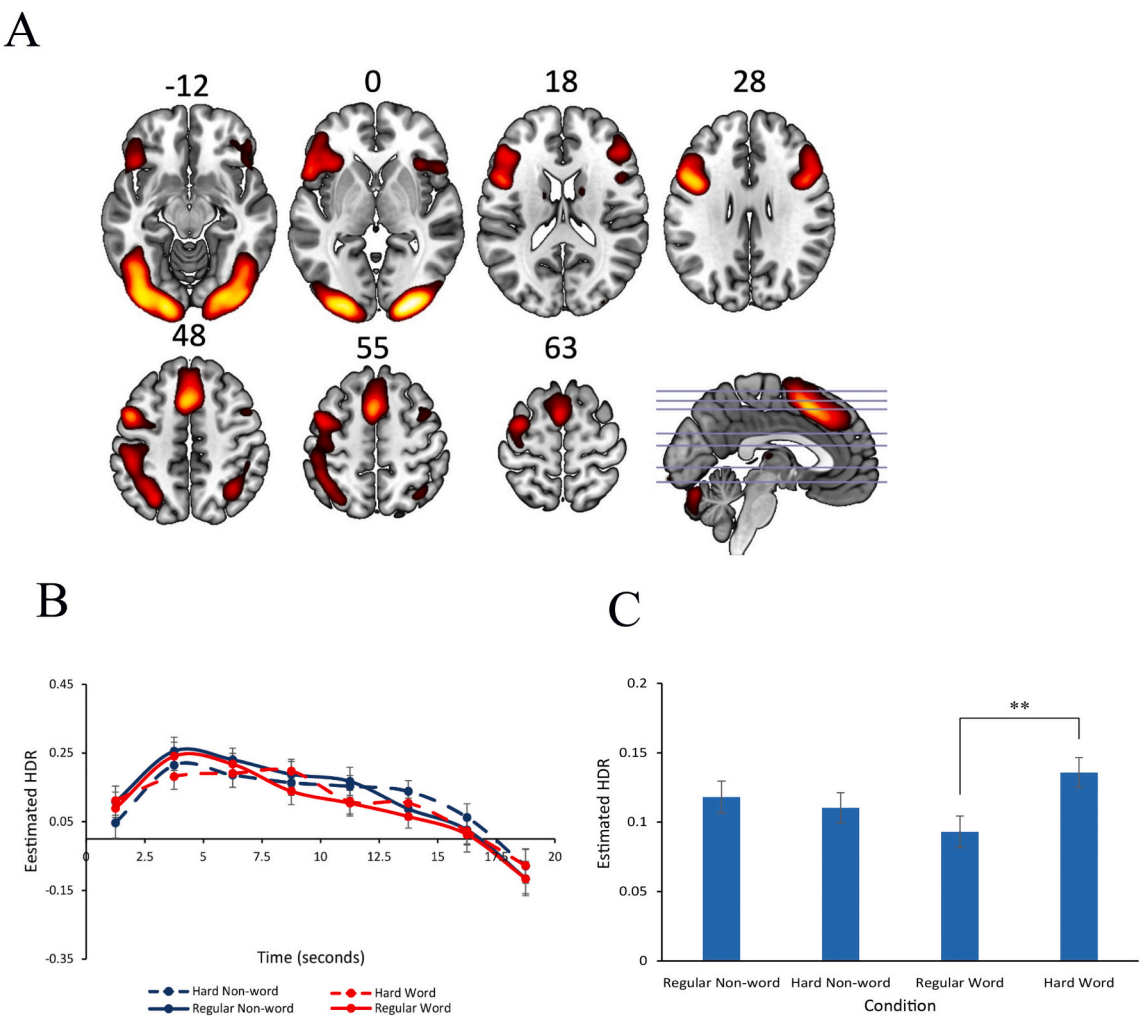

Fig. 3. A (top): Dominant 10 % of component loadings for Component 2, linguistic processing network (LPN). Montreal Neurological Institute Z-axis coordinates are displayed. Images are displayed in neurological convention (left is left). Red/yellow = positive loadings (positive threshold = 0.20, max = 0.45). B (bottom): mean finite impulse response (FIR)-based predictor weights plotted as a function of post-stimulus time (TR = 2500 ms) and condition (averaged over group; error bars are standard errors). C (bottom): mean finite impulse response (FIR)-based predictor weights averaged over time bins, plotted as a function of condition (averaged over group; error bars are standard errors; ** denotes statistically significant difference, $p < .05$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Component 1 (all *p*s > .10). Hence, the rest of the results are averaged over group. Fig. 2B and C display the estimated HDR shape by lexicality and difficulty, respectively, with predictor weights plotted as a function of post-stimulus time and condition. The ANOVAs revealed a highly significant main effect of post-stimulus time, $F(7,308) = 23.58$, $p < .001$, $\eta^2 = 0.35$, demonstrating a reliable HDR shape across the participants. The lexicality × time interaction was also highly significant, $F(7,308) = 10.33$, $p < .001$, $\eta^2 = 0.19$, and dominated by 2 × 2 interactions involving changes from time bins 1 to 2, 3 to 4, and 4 to 5 (all *p*s < .005, all $\eta^2 > 0.20$). This reflects the dip in HDR intensity visible in the word condition (Fig. 2B, solid blue line), which is absent in the non-word condition (Fig. 2B, dotted blue line). Since the DMN is comprised of negative loadings (i.e., deactivation relative to pre-stimulus baseline), this pattern of results suggests the DMN deactivates more for non-word stimuli (Fig. 2B, dotted blue line) than word stimuli (Fig. 2B, solid blue line). The interaction between difficulty × time was also significant, $F(7,308) = 3.27$, $p < .05$, $\eta^2 = 0.07$. This interaction is dominated by the change from time bin 4 to 5, $F(1, 44) = 1.12$, $p = .30$, and time bin 5 to 6, $F(1, 44) = 2.79$, $p = .10$ (Fig. 2C). Although neither of the effects from these time bins is significant, they show the source of the significant interaction is the differences in the intensities at time bin 5, whereby the hard condition (Fig. 2C, solid blue line) decreases from a higher peak and the regular condition (Fig. 2C, dotted blue line) sustains a shallower peak. This is in line with previous research showing that task related DMN deactivation is sensitive to task difficulty (Esposito et al., 2009; Woodward et al., 2013). Adding sex as a between-subjects factor did not produce additional significant effects (all *p*s > .05).

3.3.2. *Component 2: linguistic processing network*

Fig. 3A depicts the brain regions associated with Component 2. The anatomical description of Component 2 is in Table 4. See Supplementary Table S2 for correspondence of activity peaks in Component 2 with anatomical descriptions, BAs and resting state networks. Supplementary Fig. S2 shows slice comparisons between the current study and previous studies (Goghari et al., 2017; Wong et al., 2020) in our lab for Component 2. Brain regions in this component reflected a linguistic processing network (LPN), with activations in left-dominant regions, including left prefrontal regions (Broca's area, BA 44, 6) and left supramarginal gyrus (anterior division; BA 2).

Fig. 3B shows the estimated HDR shape for Component 2. There was no significant main effect of group (all *p*s > .1), therefore results reported are averaged over group. The ANOVAs revealed a highly significant main effect of post-stimulus time, $F(7,308) = 34.98$, $p < .001$, $\eta^2 = 0.44$, demonstrating a reliable HDR shape. There was a significant main

Table 4
Cluster volumes for the most extreme 10 % of Component 2 loadings (LPN), with anatomical labels, Brodmann's areas, and MNI coordinates for the peak of each sub-cluster. Clusters smaller than 270 mm^3 were omitted.

Anatomical label	Cluster volume (mm^3)	Brodmann's area for peak locations	MNI coordinate for peak locations		
			x	y	z
Positive loadings					
Cluster 1: Bilateral	104,160				
Temporal occipital fusiform cortex		37	36	−46	−23
Temporal occipital fusiform cortex		37	−42	−52	−21
Lateral occipital cortex, inferior division		19	46	−64	−15
Occipital fusiform gyrus		19	36	−66	−23
Cerebellum VIII		n/a	28	−68	−51
Occipital fusiform gyrus		18	12	−78	−23
Cerebellum crus 1		n/a	−8	−78	−23
Lateral occipital cortex, inferior division		19	−36	−90	−7
Occipital pole		18	−34	−92	−5
Occipital pole		18	28	−94	3
Occipital pole		18	−20	−96	−7
Cluster 2: Left hemisphere	62,832				
Frontal pole		45	−48	38	5
Inferior frontal gyrus, pars triangularis		45	−46	30	15
Frontal orbital cortex		38	−46	22	−7
Inferior frontal gyrus, pars opercularis		48	−54	16	1
Precentral gyrus		44	−50	10	31
Precentral gyrus		6	−50	4	45
Middle frontal gyrus		6	−40	−2	57
Middle frontal gyrus		6	−38	−4	59
Precentral gyrus		4	−36	−20	63
Precentral gyrus		3	−38	−22	51
Supramarginal gyrus, anterior division		2	−46	−34	45
Superior parietal lobule		7	−36	−54	49
Lateral occipital cortex, superior division		7	−28	−64	47
Cluster 3: Left hemisphere	22,520				
Paracingulate gyrus		32	−2	16	49
Cluster 4: Right hemisphere	15,112				
Middle frontal gyrus		45	48	32	19
Precentral gyrus		44	46	10	27
Middle frontal gyrus		6	44	6	51
Middle frontal gyrus		6	38	2	57
Cluster 5: Right hemisphere	5016				
Frontal pole		45	50	42	−5
Frontal pole		47	36	40	−13
Frontal pole		47	48	36	−13
Frontal pole		47	40	34	−15
Insular cortex		47	36	22	−1
Inferior frontal gyrus, pars triangularis		38	50	20	−5
Cluster 6: Right hemisphere	4784				
Supramarginal gyrus, posterior division		2	46	−36	45
Angular gyrus		7	36	−56	47
Cluster 7: Left hemisphere	568				
Left thalamus		n/a	−8	−16	9
Cluster 8: Right hemisphere	440				
Right caudate		n/a	14	2	15
Cluster 9: Left hemisphere	376				
Left caudate		n/a	−14	0	15

effect of difficulty, $F(1,44) = 19.12$, $p < .001$, $\eta^2 = 0.30$, with higher activation for the hard than regular condition. The difficulty × lexicality interaction was also significant, $F(1,44) = 5.30$, $p < .05$, $\eta^2 = 0.11$. This significant interaction was driven by the difficulty comparison within the word conditions such that hard had higher activation than regular in the word conditions ($p = .001$; Fig. 3C), with no significant difficulty difference for non-word, although the means were in the opposite direction, thereby contributing to the interaction. Higher activation was expected for the hard word condition based on our previously published work as the LPN showed increased activation in the hard word condition, theoretically indicating increased demand of the LPN, but also that this should not be present in the non-word condition (Wong et al., 2020). Adding sex as a between-subjects factor did not produce any significant effects (all *ps* > .05).

3.3.3. Component 3: response network

Fig. 4A depicts the brain regions that are linked with Component 3. The anatomical description of this component is in Table 5. Supplementary Table S3 shows the correspondence of activity peaks in Component 3 with anatomical descriptions, BAs and resting state networks. Supplementary Fig. S3 shows slice comparisons between the current study and previous studies (Lavigne et al., 2015, 2020) in our lab for Component 3. Activation in this network included left-dominant pre- and post-central gyri (BAs 3, 6), and juxtapositional lobule cortex (BA 6), which are often motor response network regions when performing a right-handed response. This network also had bilateral activations in the superior (BA 7, 19) and inferior (BA 18, 19, 37) divisions of the lateral occipital cortex, superior parietal lobule (BA 7), and occipital fusiform gyrus (BA 19), which are visual attention areas (Tomasi et al., 2007). This network comprising brain regions involved in motor response and visual attention suggests its involvement in both processes. Negative

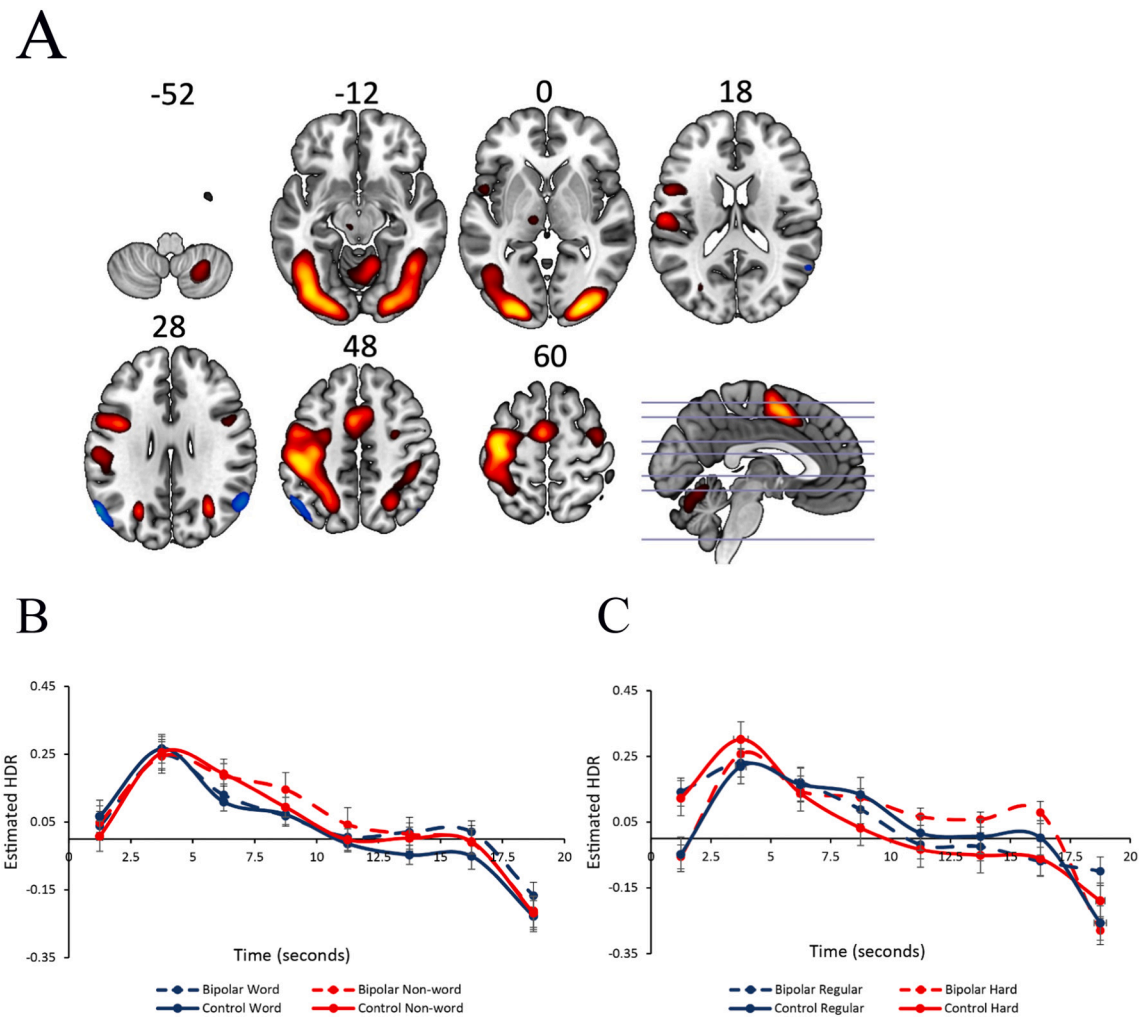

Fig. 4. A (top): Dominant 10 % of component loadings for Component 3, proposed right-handed response (RESP/DMN) network. Montreal Neurological Institute Z-axis coordinates are displayed. Images are displayed in neurological convention (left is left). Red/yellow = positive loadings (positive threshold = 0.16, max = 0.33); blue/green = negative loadings (negative threshold = −0.16, min = −0.21). B and C (bottom): mean finite impulse response (FIR)-based predictor weights by lexicality (B) and difficulty (C) of items, plotted as a function of post-stimulus time (TR = 2500 ms) and condition (averaged over participants in each group; error bars are standard errors). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

loadings in the lateral occipital cortex (BA 39) reflected DMN deactivation.

Fig. 4B and C displays the estimated HDR shape for each group for Component 3 as a function of lexicality and difficulty, respectively. The ANOVA revealed a highly significant main effect of post-stimulus time, $F(7,308) = 30.10$, $p < .001$, $\eta^2 = 0.41$, demonstrating a reliable HDR shape. Significant main effects of group, lexicality and difficulty were not observed (all $ps > .05$). There was a significant lexicality × time interaction, $F(7,308) = 4.13$, $p = .001$, $\eta^2 = 0.09$. This interaction was dominated by the change from time bin 2 to 3, where the decrease is much steeper in the word than the non-word condition. Additionally, there was a significant lexicality × time × group interaction, $F(7,308) = 2.83$, $p < .01$, $\eta^2 = 0.06$, and a significant difficulty × time × group interaction, $F(7,308) = 5.90$, $p < .001$, $\eta^2 = 0.12$. The lexicality × time × group interaction was dominated by the change from time bin 3 to 4, due to the non-word condition sustaining activity for longer in the BD group (Fig. 4B, dotted red line) but not the control group (Fig. 4B, solid red line). The difficulty × time × group interaction was dominated by the change from time bin 7 to 8, due to the hard condition activity dropping from previously sustained activity in the BD group (Fig. 4C, dotted red line), and there was no sustained activity for the control group (Fig. 4C, solid red line). Thus, both interactions were due to increased activity for the BD group.

4. Discussion

We investigated the brain networks associated with LD in people with BD using fMRI and a multidimensional analysis method. The BD and control groups did not significantly differ in RT in the LD task. Differences were observed in accuracy, with the BD group showing significantly higher accuracy than the control group in the hard condition. Attentional, response and lexical processes were captured by separate function-specific brain networks (DMN, RESP and LPN, respectively). In addition, although RT patterns showed that hard non-word was the most difficult condition, reflected by load-dependent (regular < hard) deactivation of the DMN in both word and non-word conditions, the LPN reflected this pattern only in the word condition (see Fig. 3C); this replicates the results of our previous study in healthy adults (Wong et al., 2020). Significant differences between BD and control groups were observed in the RESP network, with the BD group showing higher activation in the non-word and hard conditions relative to the control group.

As BD is associated with deficits in language, attention and psychomotor function (Bora et al., 2009; Raucher-Chéné et al., 2017), we expected the BD patients to have impaired LD task performance. However, contrary to our prediction, the patients had better accuracy than the control group in the LD task. The proportion of native English speakers

Table 5
Cluster volumes for the most extreme 10 % of Component 3 loadings (RESP), with Harvard-Oxford anatomical labels, Brodmann's areas, and MNI coordinates for the peak of each sub-cluster. Clusters smaller than 270 mm^3 were omitted.

Anatomical label	Cluster volume (mm^3)	Brodmann's area for peak locations	MNI coordinates for peak locations		
			x	y	z
Positive loadings					
Cluster 1: Bilateral	94,368				
Temporal occipital fusiform cortex		37	38	−42	−23
Temporal occipital fusiform cortex		37	−40	−50	−19
Cerebellum Vi		37	24	−52	−23
Inferior temporal gyrus, temporooccipital part		37	44	−58	−13
Lingual gyrus		18	10	−58	−13
Cerebellum VIII		n/a	24	−58	−49
Lingual gyrus		19	−18	−60	−17
Cerebellum VI		19	−28	−62	−23
Lateral occipital cortex, inferior division		37	−44	−66	−9
Cerebellum VIII		n/a	20	−66	−47
Occipital fusiform gyrus		19	42	−66	−17
Cerebellum VI		n/a	8	−70	−19
Cerebellum crus 1		n/a	−8	−72	−21
Cerebellum crus 2		n/a	6	−72	−31
Lateral occipital cortex, inferior division		19	−42	−78	−9
Lateral occipital cortex, inferior division		19	40	−82	−5
Lateral occipital cortex, inferior division		19	−36	−86	−7
Occipital pole		18	26	−90	−5
Lateral occipital cortex, inferior division		18	−30	−90	−5
Occipital pole		18	−24	−92	−5
Cluster 2: Bilateral	87,528				
Temporal pole		38	−52	8	−3
Precentral gyrus		44	−42	4	27
Precentral gyrus		6	−52	4	31
Precentral gyrus		48	−52	4	13
Juxtapositional lobule cortex (formerly supplementary motor cortex)		6	−4	2	53
Precentral gyrus		6	−52	−4	47
Juxtapositional lobule cortex (formerly supplementary motor cortex)		6	8	−4	69
Central opercular cortex		48	−40	−4	13
Middle frontal gyrus		6	−30	−6	53
Precentral gyrus		6	−40	−12	63
Central opercular cortex		48	−58	−18	19
Postcentral gyrus		2	−48	−28	45
Postcentral gyrus		3	−38	−34	63
Superior parietal lobule		7	−28	−48	45
Superior parietal lobule		7	−24	−50	63
Lateral occipital cortex, superior division		19	−24	−66	31
Lateral occipital cortex, superior division		19	−26	−68	29
Cluster 3: Right hemisphere	12,128				
Supramarginal gyrus, posterior division		2	44	−36	47
Postcentral gyrus		2	40	−38	61
Superior parietal lobule		40	30	−46	43
Lateral occipital cortex, superior division		7	26	−60	47
Lateral occipital cortex, superior division		19	30	−64	29
Cluster 4: Right hemisphere	6568				
Precentral gyrus		44	52	8	31
Precentral gyrus		44	46	4	29
Precentral gyrus		6	58	2	39
Precentral gyrus		6	46	−4	55
Precentral gyrus		6	40	−6	61
Precentral gyrus		6	30	−6	51
Superior frontal gyrus		6	24	−8	71
Cluster 5: Left hemisphere	2168				
Left thalamus		n/a	−10	−18	7
Brainstem		n/a	−8	−24	−9
Cluster 6:	624				
Cerebellum VIII		n/a	−32	22	5
Cluster 7: Left hemisphere	560				
Cerebellum VIII		n/a	−18	−70	−47
Negative loadings					
Cluster 1: Left hemisphere	7360				
Lateral occipital cortex, superior division		39	−54	−60	43
Lateral occipital cortex, superior division		39	−58	−68	29
Lateral occipital cortex, superior division		39	−48	−70	41
Lateral occipital cortex, superior division		39	−42	−72	49
Lateral occipital cortex, superior division		39	−52	−74	33
Lateral occipital cortex, superior division		19	−40	−78	39
Cluster 2: Right hemisphere	4312				

(*continued on next page*)

Table 5 (*continued*)

Anatomical label	Cluster volume (mm^3)	Brodmann's area for peak locations	MNI coordinates for peak locations		
			x	y	z
Lateral occipital cortex, superior division		39	58	−60	25
Lateral occipital cortex, superior division		39	54	−66	33

was higher in the BD than the control group, which might explain the higher accuracy of the BD group in the LD task. However, we did not have a large enough sample to analyze English mastery as a factor in the current study. The reliability of our findings might also be weak due to a ceiling effect. Further studies with larger samples are needed to test the replicability of our findings.

Component 1 was associated with deactivations in brain regions associated with the DMN, including the precuneus (BA 17), frontal pole (BA 46) and angular gyrus (BA 39; Buckner et al., 2008). This network deactivated more for the non-word condition than the word condition, and for the hard condition than the regular condition. The DMN was also extracted in our previous fMRI study of this LD task with healthy adults (Wong et al., 2020) and was also found to deactivate more for the non-word and hard conditions than for the word and regular conditions. These findings are in line with the results of numerous studies that have found DMN deactivation to be sensitive to task difficulty (Cheng et al., 2020; Esposito et al., 2009; Woodward et al., 2013, 2015) and may reflect the engagement of attentional processes and the suppression of task-irrelevant functions supported by the DMN such as mind-wandering (Anticevic et al., 2010).

The BD and control groups did not significantly differ in DMN activity in the current study. While, to our knowledge, this is the first study to examine DMN activity in BD during the LD task, some previous studies have assessed DMN activity in BD using other language tasks (Allin et al., 2010; Costafreda et al., 2011). Costafreda et al. (2011) used a verbal fluency task and fMRI to investigate the neurophysiology underlying language impairments in euthymic BD patients compared to patients with schizophrenia and healthy controls. Both patient groups showed greater activity in the bilateral precuneus, posterior cingulate and angular gyrus than the control group, indicating a failure to deactivate the DMN. DMN deactivation has been shown to be predictive of task error, with lower deactivation preceding errors in cognitive tasks (Bednarski et al., 2011; Li et al., 2007). Hence, although DMN overactivity in BD may contribute to impaired task performance, no evidence for this was observed in the current study.

Component 2 (LPN) involved activations in language related areas, including prefrontal regions (Broca's area, BA 44, 47, 6), supramarginal gyrus (anterior division, BA 2) and angular gyrus (BA 7). The LPN was also extracted in our previous fMRI study of this LD task in healthy adults (Wong et al., 2020). The brain regions that load on the LPN have been shown by numerous studies to be involved in language (Devlin et al., 2003; Frost et al., 1999; Gold et al., 2006; Lavigne et al., 2015; Lavigne and Woodward, 2018; Price et al., 1997; Woodward et al., 2015). For instance, Broca's area has long been identified as an important area for language (see for review Flinker and Knight, 2018). The supramarginal gyrus and angular gyrus have been found to be preferentially involved in phonological and semantic processing, respectively (Devlin et al., 2003; Hartwigsen et al., 2016; Price et al., 1997).

A significant difference in LPN activation was not observed between the BD and control groups. As such, the higher accuracy of the BD group in the LD task does not appear to be substantially accounted for by differences in LPN activity. The few studies that have investigated activation in language regions in BD have generally found altered activity in these regions (Curtis et al., 2007; Lv et al., 2016). Curtis et al. (2007) investigated language processing in euthymic BD using fMRI and various language tasks. Both the BD and control groups showed activation in language related brain regions. However, across all the language tasks, the BD group showed increased activation in the left prefrontal cortex and in a bilateral cerebellum/fusiform/lingual gyrus cluster compared to the control group. It should be noted that the Curtis et al. (2007) study is also limited by its small sample size. Further studies with larger samples are needed to test the replicability of our findings.

Component 3 (RESP) comprised brain regions that are primarily involved in motor response and visual attention processes. The RESP was extracted in our previous fMRI study of the LD task in healthy adults (Wong et al., 2020) and has been observed in studies using various tasks that require a motor response (Hanakawa et al., 2008; Lavigne et al., 2020, 2016, 2015; see Supplementary Fig. S3). Hanakawa et al. (2008) used fMRI to examine brain activity during a finger-tapping task in which participants were cued to either physically perform a finger-tapping sequence or imagine themselves performing the sequence. Movement-related activity was observed in a distributed network that included the left pre- and post-central gyri, right superior frontal gyrus, right superior parietal lobule, and left thalamus, which are all regions that were extracted as part of the RESP in the current study (see Table 5). Visuo-attentional processes being captured on the RESP might explain our finding of a steeper decrease in RESP activity in the word than non-word condition. The non-word condition was associated with a slower RT than the word condition, indicating that it was more difficult and thus, placed more demand on visuo-attentional processes than the word condition.

The increased activation in the BD group relative to the control group in the RESP network for the non-word and hard conditions may be a trait- or state-related feature of BD. Caligiuri et al. (2003) examined possible associations between affective state and cortical and subcortical activity in BD using fMRI and a motor task that required subjects to flex their thumb as quickly as possible in response to a visual cue. Patients in the manic and depressive states of BD were both found to have elevated activity in cortical and subcortical motor regions, with the patients in the manic state showing greater activity than the control group in the left juxtapositional lobule cortex, left globus pallidus, and right primary motor cortex, while patients in the depressive state had higher activity than the control group in the right primary motor cortex. Bipolar mania was associated with higher activity in the globus pallidus than bipolar depression, whereas bipolar depression was linked with higher activity in the thalamus and caudate than bipolar mania (Caligiuri et al., 2003). Moreover, patients who were off antipsychotics and mood-stabilizers showed significantly higher activation throughout motor regions of the brain than patients who were on medications. These findings suggest that BD might be associated with hyperactivity in motor response regions. The results also suggest that overactivity in some motor response regions may be present irrespective of the affective state of BD (i.e., trait-related features of BD), while activity in other motor response areas might only be high in some states of BD. Overactivity in motor response networks in BD could be related to a disturbance of inhibitory processes regulating motor behaviour, which has often been associated with bipolar mania (Caligiuri et al., 2003; Mazzola-Pomietto et al., 2009).

4.1. Limitations

The current study has some notable limitations. First, our small sample makes it difficult to determine if our outcomes are replicable. For instance, it is possible that we did not have enough power to detect significant group differences in RT and in DMN and LPN activations

because of the small sample. The small sample size also precluded us from examining if English mastery was a factor in our analyses. Due to the small sample, we also could not make comparisons between the patients to determine if LD task performance and activity in the functional networks differed based on the BD state; this may have helped to determine if RESP overactivity is trait- or state-related in BD. Last, the LD stimuli were presented in succession very rapidly, which resulted in nonstandard HDR shapes due to insufficient relaxation of the HDR between trials.

5. Conclusion

In summary, three functional brain networks (DMN, LPN and RESP) were identified in BD patients and controls during LD. Contrary to our prediction, the BD group had better performance than the control group in the LD task. Significant differences in DMN and LPN activity were not found between the two groups. The BD patients had higher activations in the RESP than controls for the non-word and hard conditions. Increased RESP activation might underlie psychomotor disturbances in BD. Specifically, psychomotor agitation is a common symptom of bipolar mania, but also occurs in bipolar depression (Judd et al., 2012; Serra et al., 2019) and might be related to increased RESP network activity. The increase in RESP activation may stem from a breakdown of inhibitory processes regulating motor behaviour in BD. Further research is needed to elucidate the underlying mechanisms for higher RESP activation in BD and to determine if psychomotor agitation in BD is related to increased RESP activity.

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Credit authorship contribution statement

All authors who meet criteria for authorship are listed as authors in the manuscript and declare that they have sufficiently participated in the research and/or preparation of the article to take public responsibility for the content. The conception and design of the study were done by Vina Goghari and Todd Woodward. Acquisition of data was mainly done by Vina Goghari. All authors contributed to the analysis and interpretation of the data. The drafting of the manuscript was mainly done by Mavis Kusi, with contributions from Samantha Wong and Todd Woodward. All authors were involved in revising the manuscript and have approved the final article that is being submitted to this journal.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2022.08.040.

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