Research paper

Anticipatory cues in emotional processing shift the activation of a combined salience sensorimotor functional network in drug-naïve depressed patients

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ARTICLE INFO

ABSTRACT

Background: Major depressive disorder is characterized by a large-scale brain network dysfunction, contributing to impairments in cognitive and affective functioning. Core regions of default mode, limbic and salience networks are also impaired in emotional processing and anticipation. This study aimed to explore default mode, salience, and limbic networks modulation during the processing of emotional stimuli with and without anticipatory cues in depression, and further investigate how these networks were functionally coupled with the rest of the brain.
Methods: Twenty-one drug-naïve depressed patients and 15 matched controls were included in the study. All participants completed a psychological assessment and the affective pictures paradigm during an fMRI acquisition. Group independent component analysis and psychophysiological interactions analyses were performed.
Results: A significant interaction between Cue, Valence and Group was found for the salience/sensorimotor network. When processing uncued emotional stimuli, patients showed increased activation of this network for negative vs. neutral pictures, whereas when anticipatory cues were displayed previously to the picture presentation, they invert this pattern of activation (hyperactivating the salience/sensorimotor network for positive vs. neutral pictures). Patients showed increased functional connectivity between the salience/sensorimotor network and the left amygdala as well as the right inferior parietal lobule compared to controls when processing uncued negative pictures.
Limitations: The sample size was modest, and the salience/sensorimotor network included regions not typically identified as part of salience network. Thus, this study should be replicated to further interpret the results.
Conclusions: Anticipatory cues shift the pattern of activation of the salience/sensorimotor network in drug-naïve depressed patients.

1. Introduction

Major Depressive Disorder (MDD) is a widely common mental disorder, affecting nearly 300 million people (GBD 2019 Mental Disorders Collaborators, 2022). It is estimated that its prevalence increased 30 % due to the COVID-19 pandemic, leading to an even greater personal, social, and economic burden (COVID-19 Mental Disorders Collaborators, 2021). The two hallmark features of this disorder are persistent depressed mood and anhedonia (American Psychiatric Association, 2013). According to cognitive theories, these symptoms are developed and maintained by negative cognitive biases in attention, processing, and memory, impacting on the emotional experience of patients with MDD (Disner et al., 2011).

Throughout the years, magnetic resonance imaging (MRI), a non-invasive tool, has been used to investigate the depressed brain in vivo, shedding light into the pathophysiology of MDD. Meta-analyses of distinct MRI modalities have consistently reported structural and functional alterations associated with this disorder in cortical-subcortical circuits (Groenewold et al., 2013; Jiang et al., 2017; Kaiser et al., 2015; Li et al., 2020; Zhang et al., 2013; Zhong et al., 2016). More recently, MDD has been perceived as a large-scale network dysfunction (Kaiser et al., 2015; Li et al., 2018; Yang et al., 2021), involving networks such as default mode (DMN), salience, and limbic networks at rest (Luo et al., 2021; Manoliu et al., 2014; Pannekoek et al., 2014; Veer, 2010) and during tasks (Shi et al., 2015; Yang et al., 2016; Zhang et al., 2017). Notably, these networks include brain regions that are involved in the processing and anticipation of emotional stimuli, such as the insula, anterior cingulate cortex (ACC), medial prefrontal cortex, and amygdala (Abler et al., 2007; Anand et al., 2005; Diener et al., 2012; Feeser et al., 2013; Groenewold et al., 2013; Hamilton et al., 2012; Herwig et al., 2010).

A meta-analysis exploring the neural correlates of emotional processing in MDD revealed opposite patterns of activation in the amygdala, insula, ACC, parahippocampal gyrus, and cerebellum in depressed patients when processing negative and positive stimuli (Groenewold et al., 2013). Specifically, patients displayed increased activation for negative stimuli and decreased for positive stimuli compared to controls, reflecting the negative bias on information processing (Disner et al., 2011; Groenewold et al., 2013). Moreover, patients showed decreased activity in the dorsolateral prefrontal cortex and increased activity in the orbitofrontal cortex for negative and positive stimuli, respectively. Interestingly, alterations in similar regions, such as the prefrontal cortex, ACC, and amygdala, were also found when anticipating negative stimuli in depression (Abler et al., 2007; Feeser et al., 2013; Herwig et al., 2010; Rosenblau et al., 2012). However, heterogeneous findings have been reported regarding the direction of the alterations on these regions, as well as the anticipation of positive stimuli (Abler et al., 2007; Feeser et al., 2013; Herwig et al., 2010). Different hypotheses have been raised to interpret these results, supporting either the negative cognitive biases described in cognitive theories (Abler et al., 2007; Herwig et al., 2010), or the emotion-context insensitivity theory (Feeser et al., 2013). Nonetheless, a normalization after antidepressant treatment has been shown for these abnormal patterns of neural activity in prefrontal cortex, ACC, and amygdala (Delaveau et al., 2011; Rosenblau et al., 2012; Wessa and Lois, 2015).

Overall, the studies described above employed voxel-wise general linear model (GLM) analyses, a commonly used method to analyse task-fMRI data given the simplicity of its implementation, interpretation, and computation (Soares et al., 2016). This approach convolves the stimulus onsets and duration with the hemodynamic response function, estimating the signal for the conditions of interest, and then statistical tests for each voxel are performed to determine the voxels with significant activation (Soares et al., 2016). Nevertheless, this requires the application of GLM models to every voxel of the brain, and subsequently the correction for these multiple comparisons, contributing to negative findings in task-based fMRI (Xu et al., 2013). To overcome those limitations, data-driven network analyses, such as independent component analysis (ICA), have been recommended to better understand the brain functional organization in neuropsychiatric disorders, and bring new insights into this field during task-based fMRI (Kaiser et al., 2015; Xu et al., 2013; Yang et al., 2021). ICA is a widely used network analysis technique that, in the context of task-fMRI, enables to investigate how functional networks are modulated by experimental factors (Barrós-Loscertales et al., 2020; Costumero et al., 2017; Kim et al., 2009; Picó-Pérez et al., 2022). This approach assumes that spatially independent regions, that are temporally correlated, form a functional connected network (Calhoun et al., 2001; Lv et al., 2018).

In the present study, 21 drug-naïve depressed patients and 15 age, sex, and education matched controls performed the affective pictures paradigm during an fMRI acquisition. We aimed to explore DMN, limbic and salience networks modulation during the processing of emotional stimuli with and without anticipatory cues in drug-naïve depressed patients, employing a data-driven network-based approach (ICA). These analyses were focused on DMN, limbic and salience networks given their overall involvement in emotional processing (Riedel et al., 2018) and their dysfunctional pattern in MDD (Abler et al., 2007; Diener et al., 2012; Feeser et al., 2013; Groenewold et al., 2013; Zhang et al., 2017). Furthermore, we aimed to investigate the functional connectivity (FC) between these networks and the rest of the brain. Finally, exploratory secondary analyses were performed to investigate the association of the networks' activation with the severity of depression and suicidal ideation in patients.

2. Methods

2.1. Ethics

This study was conducted in accordance with the Declaration of Helsinki (59th amendment) and was approved by the Ethics Committees of the University of Minho (Braga, Portugal) and Hospital de Braga (Braga, Portugal). All participants provided written informed consent after all the objectives and procedures were explained.

2.2. Participants

Thirty-two outpatients diagnosed with MDD were recruited at Hospital de Braga (Braga, Portugal). To be included in the study, patients had to be aged 18–65 years old, present MDD diagnosis without psychotic features and have no prior history of antidepressant treatment (i.e., drug-naïve). The diagnosis was confirmed by an experienced psychiatrist using the Structured Clinical Interview for DSM-IV-TR (First and Gibbon, 2004). Controls (n = 19) were recruited from the general community, and were age, sex and education matched to the patients' group, with no sign of any psychiatric disorder nor under psychotropic medication. Participants were enrolled in the study between January 2016 and January 2020.

For both groups, participants were excluded if they had any MRI contraindication, comorbid psychiatric disorders (also the presence of MDD for the control group), prior medical history of neurological or traumatic brain injury, and any sign of cognitive impairment defined as a Mini Mental State Examination score below 24 (Folstein et al., 1975; Guerreiro et al., 1994). Following these criteria, 9 patients and 4 controls were excluded due to MRI contraindications (n = 3), brain lesions or artifacts in the acquired images (n = 4), lost scans (n = 1), and technical issues with the task during the fMRI acquisition (n = 5). Thus, 23 MDD and 15 controls were included in the analysis. Patients' data on other MRI modalities has been previously reported (Reis et al., 2022; Vieira et al., 2021).

2.3. Measures and procedure

2.3.1. Clinical assessment

In the same day of the MRI acquisition, all participants were assessed using the following instruments: Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960), Hamilton Anxiety Rating Scale (HARS) (Hamilton, 1959), Beck Scale for Suicide Ideation (BSSI) (Beck and Steer, 1991). These instruments assessed depression and anxiety severity, and suicidal ideation, respectively.

2.3.2. Affective pictures paradigm

During the fMRI acquisition, participants performed the affective pictures paradigm (Friedel et al., 2009), previously used to investigate

emotional processing and anticipation in depression (Friedel et al., 2009; Rosenblau et al., 2012). One hundred and eight emotionally evocative pictures (36 positive, 36 negative and 36 neutral valence), selected from the International Affective Picture Set (IAPS) database (Lang et al., 2005), were displayed on a screen using E-Prime 3.0 (Psychology Software Tools, Inc., USA) with an event-related design.

The pictures were presented for 2 s in a pseudo-random order with a pseudorandomly jittered inter-session interval of 1.6–3 s to sample the hemodynamic response at different data points (Friedel et al., 2009). Before each picture, a cue was presented for 0.5 s followed by a fixation cross. In half of the trials, the pictures were cued by a word (positive, negative, or neutral) indicating their emotional valence (cued condition), and in the other half the pictures were cued with a meaningless combination of letters ("dghntfu"), that did not predict their emotional valence (uncued condition) (see Fig. 1). These conditions were counterbalanced across subjects to remove any effects of temporal order when displaying the pictures to the participants (Friedel et al., 2009).

Participants were instructed to passively view the pictures, given the influence of active emotional rating tasks in brain activation patterns, and press a button with their right index finger whenever a picture was displayed on the screen to avoid attentional losses (Friedel et al., 2009).

2.3.3. MRI data acquisition and pre-processing

A clinically approved Siemens Magnetom Avanto 1.5 T scanner (Siemens Medical Solutions, Erlangen, Germany) equipped with a 12-channel receive-only cerebral antenna was used to acquire the MRI data. All patients underwent the same acquisition protocol including several different acquisitions. T1-weighted images were acquired using a magnetisation-prepared rapid gradient echo sequence with 176 slices, voxel resolution $1.0 \times 1.0 \times 1.0$ mm, field of view (FOV) 234×234 mm2, flip angle (FA) of 7°, echo time (TE) of 3.48 ms, and repetition time (TR) of 2730 ms for anatomical reference. Functional images were acquired during the affective pictures paradigm using echo-planar imaging sequences sensitive to blood-oxygenation-level dependent contrast with the following parameters: 38 slices, slice thickness 5 mm, FOV 256×256 mm2, TR 2500 ms, TE 30 ms, interslice time 83 ms, FA 90°, and 64×64 imaging matrix.

The raw acquisitions from all the participants were visually checked to discard any brain lesions, critical head motion, or artifacts that could compromise the data.

Structural and functional images were pre-processed using FMRIPREP version 20.2.5 (RRID:SCR_016216) (Esteban et al., 2019), a Nipype (RRID:SCR_002502) based tool (Gorgolewski et al., 2011). Preprocessing is detailed in the Supplementary Material.

2.4. Statistical analysis

2.4.1. Demographic and clinical data

Demographic and clinical data were analysed using Statistical Package for the Social Sciences (SPSS) software (version 27; IBM Corp., Armonk, NY, USA). Normality and homogeneity of variances were assessed in both groups using Shapiro-Wilk and Levene tests, respectively. Comparisons between groups were performed using independent sample *t*-tests (or Mann-Whitney tests, when variables did not follow a normal distribution), and chi-squared tests (χ^2) for categorical variables. p-values under .05 were considered statistically significant.

2.4.2. fMRI first-level analyses

First-level analyses were performed using Statistical Parametric Mapping 12 software (SPM12; Wellcome Trust Center for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm). Pictures valence (positive, negative, and neutral) and cues (positive, negative, neutral and "dghntfu") were included as explanatory variables in the model and convolved with the canonical hemodynamic response function. A high-pass filter of 128 s was used. The mean corticospinal fluid and white-matter signals, as well as the first 6 aCompCor components, framewise displacement and DVARS (i.e., noise-related variables computed during FMRIPREP; see Supplementary Material) were used as regressors. The contrasts of interest defined were Negative > Neutral Uncued, Positive > Neutral Uncued, Negative > Neutral Cued, and Positive > Neutral Cued, including only picture presentation time periods.

2.4.3. ICA

Group ICA (Calhoun et al., 2001) was performed with the Gift toolbox (version 3.0c, http://icatb.sourceforge.net) using the Infomax algorithm (Bell and Sejnowski, 1995). First, voxel intensity was normalized, and all the data were pooled into a single dataset through a two-step data reduction approach using principal component analysis. Then, 30 independent components were selected to input ICA, based on the minimum description length criteria (Li et al., 2007). Fifty ICA iterations were performed by ICASSO (Himberg et al., 2004) to ensure stability of the estimated components. Finally, individual component maps and time courses were estimated using a group ICA 3 back-reconstruction approach. The components resulting from ICA represent group components, the back-reconstruction step is applied to go back to the subject-level. Group ICA based back-reconstruction methods use the aggregate components of ICA and the results from the data reduction step to compute the individual subject components, and among these GICA3 provides the most robust and accurate results with an intuitive interpretation (Erhardt et al., 2011).

Fig. 1. Affective pictures paradigm.

2.4.4. Analysis of the component spatial maps

The spatial maps created by ICA were used to determine the brain regions significantly related to each component time course, through a second level analysis performed with SPM12 at family-wise error (FWE)-corrected p < .05. Regarding this study hypothesis, the networks of interest were DMN, salience, and limbic networks, and they were visually identified taking into consideration the presence of core regions of these networks.

2.4.5. Analysis of the component time courses

GLM was applied on the individual component time courses using a design matrix modelling the conditions of the affective pictures paradigm described above. These analyses yielded a set of beta-weights representing the modulation of component time courses by the GLM regressors. Two patients were excluded from further analysis as they were considered extreme outliers (beta-weights z-score > 3.29) for at least one network of interest. Then, separate second-level group analyses were performed for the contrasts of interest, using the estimated beta-weights.

Group analyses were performed in SPSS using a mixed design ANOVA with one between-subjects factor (group, 2 levels: MDD patients and controls), and 2 within-subjects factors (Valence, 2 levels: Positive > Neutral and Negative > Neutral; and Cue, 2 levels: Uncued and Cued). Benjamini-Hochberg false discovery rate (FDR) correction was used to correct for the comparison of multiple networks. Additionally, exploratory analyses were performed to investigate the association between the networks' activation and the severity of depression and suicidal ideation in patients using Pearson's (*r*) correlation (or Kendall's tau (τ) correlation when variables did not follow a normal distribution). p-values under .05 were considered statistically significant. Correlations were not corrected for multiple comparisons; thus, any significant correlation results should be considered preliminary.

2.4.6. Psychophysiological interactions analyses

Psychophysiological interactions (PPI) analyses were performed using SPM12 to explore the functional coupling between task-dependent networks showing statistically significant differences and the rest of the brain (the 'physiological' factor), as a product of each condition of interest (the 'psychological' factor).

First, binary masks of each the network showing statistically significant results in the previous analyses were created using SPM12 tools. These masks were used as a region of interest for every contrast of interest, for each one of the participants. Then, FC maps were estimated for each seed (network with significant results in the previous analysis) and contrast using whole-brain linear regression analyses. Contrast images were generated for each subject by estimating the regression coefficient between the seed time series and each brain voxel signal. At second level analyses, independent sample *t*-tests were performed for each contrast of interest to investigate differences between the groups. Statistical significance was set using SPM12 cluster thresholding correction with an uncorrected voxel p-value of .001, and an FWE-corrected cluster p-value of .05.

3. Results

3.1. Demographic and clinical characterization

Demographic and clinical characteristics of the participants included in the final analyses are displayed in Table 1.

3.2. ICA results

3.2.1. Networks of interest identified

The networks of interest were visually identified from the 30 independent components. The DMN mainly included the medial prefrontal

Table 1
Demographic and clinical characterization of the groups. Data is represented by mean ± standard deviation or median (interquartile range), for normally distributed and non-normally distributed variables, respectively.

	MDD patients (n = 21)	Controls (n = 15)	Statistics
Age (years)	37.00 (23.00)	26.00 (10.00)	$U = 109.50$, p = .125, $r = -0.257$
Sex (male/ female)	8/13	5/10	$\chi^2 = 0.09$, p = .769, $\phi = 0.049$
Education (years)	11.52 ± 4.78	14.40 ± 4.34	$t(34) = 1.85$, p = .073, $d = 0.625$
HDRS score	22.00 (15.00)	1.00 (2.00)	$U = 0.00$, p < .001, $r = 0.000$
HARS score	23.71 ± 9.45	1.60 ± 1.18	$t(20.87) = -10.61$, p < .001, $d = -3.034$
BSSI score[a]	1.00 (7.00)	0.00 (0.00)	$U = 63.00$, p = .004, $r = -0.557$

MDD, Major Depressive Disorder; HDRS, Hamilton Depression Rating Scale; HARS, Hamilton Anxiety Rating Scale; BSSI, Beck Scale for Suicide Ideation .
[a] One control with missing data.

cortex, precuneus, and anterior and posterior cingulate cortex; the limbic network comprised the amygdala, hippocampus and parahippocampal gyrus; and the salience network included ACC, insula, postcentral and precentral gyrus (see Fig. S1). The salience network, including motor regions, was considered in this study given the previously reported difficulty to disentangle it from other networks in task-based fMRI due to its co-activations with other brain regions (Menon, 2015). However, as it includes core regions of both salience and sensorimotor networks, hereafter this network will be referred to as salience/sensorimotor (S/SM) network.

3.2.2. Group analyses

A statistically significant interaction between Group, Valence and Cue was found in the S/SM network ($F(1,34) = 6.394$, p = .016, $p_{FDR-corr} = 0.048$, $\eta_p^2 = 0.158$). For uncued pictures, patients presented higher activation when observing negative vs. neutral pictures compared to when they observed positive vs. neutral pictures, whereas the opposite pattern was displayed by controls (Fig. 2). For cued pictures, patients had higher activation when observing positive vs. neutral pictures than when observing negative vs. neutral pictures, and the controls had a similar activation pattern for both contrasts (Fig. 2). No other statistically significant interactions nor main effects were found for this network.

For DMN and limbic networks, no statistically significant main effects nor interactions were found. Detailed statistics of the non-significant results are displayed in the Supplementary Material.

The exploratory analyses revealed a significant negative correlation between the DMN activation for positive vs. neutral uncued pictures and the suicidal ideation score ($\tau = -0.423$, p = .011) (Fig. S2). No other statistically significant correlations were found.

3.3. PPI results

As the S/SM network revealed a statistically significant interaction between Group, Valence, and Cue (Fig. 2), PPI analyses were performed using a mask of this network as a seed.

When observing negative vs. neutral uncued pictures, patients showed increased FC between the S/SM network and the left amygdala and the right inferior parietal lobule (IPL) compared with controls (Table 2, Fig. 3). No statistically significant between-group differences were found for the other contrasts.
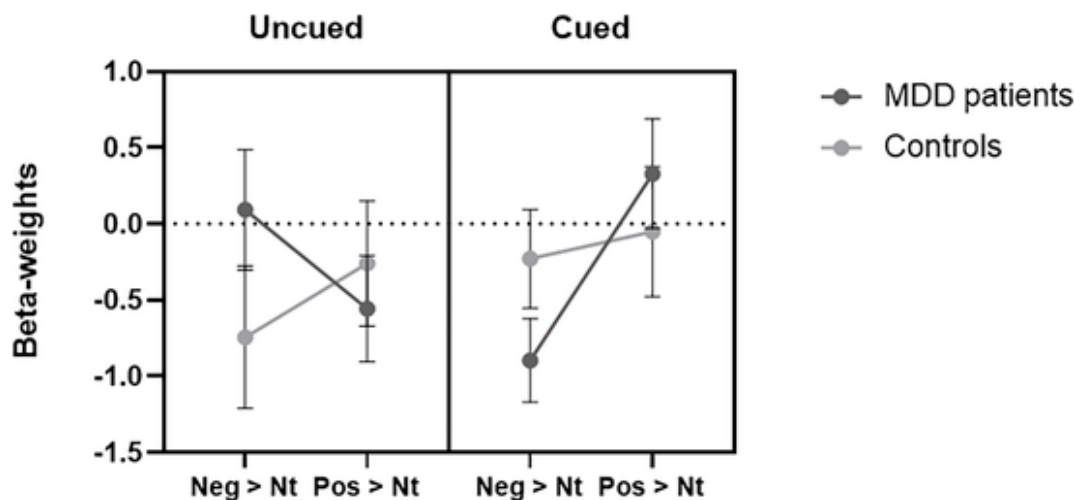
Fig. 2. Statistically significant interaction between Group, Valence, and Cue. For uncued pictures, patients showed an increased activation of the S/SM network when observing negative vs. neutral pictures compared with observing positive vs. neutral pictures. Controls showed the opposite pattern of activation than patients. For cued pictures, patients increased the activation of the S/SM network when observing positive vs. neutral pictures than negative vs. neutral pictures, and the controls had a similar activation pattern for both contrasts. MDD, major depressive disorder; Neg, negative; Pos, positive; Nt, neutral.

Table 2

Brain regions showing statistically significant increased connectivity with the S/SM network seed in MDD patients compared to controls while observing negative vs. neutral uncued pictures (whole-brain uncorrected voxel $p < .001$, and FWE-corrected cluster $p < .05$).

Contrast	Brain regions	MNI coordinates at signal peak			Cluster size (voxel)	t-value
		x	y	z		
Negative > Neutral Uncued						
MDD patients > Controls	L Amygdala	−19	−4	−16	41	5.67
	R IPL	54	−34	39	42	4.46

Note: MNI, Montreal Neurological Institute; MDD, Major Depressive Disorder; L, left; R, right; IPL, inferior parietal lobule.

4. Discussion

This study explored the DMN, limbic and S/SM networks modulation during the processing of emotional stimuli with and without anticipatory cues in a sample of drug-naïve depressed patients, using ICA. Our findings revealed that S/SM activation was shifted during the processing of emotional stimuli with anticipatory cues in these patients. PPI analyses were employed to investigate the functional coupling between this network and other regions of the brain, showing an increased FC between S/SM and the left amygdala and the right IPL when processing uncued negative pictures in patients compared with controls.

The salience network, whose prominent nodes are the ACC and the insula, is responsible for attending to emotionally salient external or internal information and coordinate the switching between large-scale brain networks in response to them (Menon and Uddin, 2010; Riedel et al., 2018). When processing emotional stimuli, patients presented an increased activation of the S/SM for negative uncued pictures compared to positive uncued pictures (vs. neutral ones), whereas controls showed the opposite pattern. Consistent with our findings, previous studies have shown a hyperactivation for negative stimuli (Groenewold et al., 2013; Hamilton et al., 2012) and hypoactivation for positive stimuli (Groenewold et al., 2013; Y. Yang et al., 2016) in the ACC and the insula in patients with MDD during emotional processing tasks. Accordingly, previous eye-tracking studies have also reported that depressed patients show an increased attention maintenance for negative pictures

and decreased for positive pictures when compared to controls (Suslow et al., 2020). Altogether, these findings seem to support the presence of mood-congruent biases in depression, that affect emotional processing, and consequently maintain depressive symptoms (Disner et al., 2011).

Unexpectedly, when patients could anticipate the valence of the stimuli displayed, the pattern of activation in the S/SM network was reversed, increasing its activation for positive pictures compared to negative (vs. neutral pictures). Differently, previous studies using similar emotional paradigms reported increased activation of the amygdala when anticipating negative stimuli (Abler et al., 2007; Rosenblau et al., 2012) and decreased activation in the prefrontal cortex for the anticipation of both positive and negative stimuli (Feeser et al., 2013). Moreover, Zhang et al. (2017) found that depressed patients had increased activity in DMN during the anticipation of positive stimuli. However, we did not find statistically significant results for DMN nor limbic networks. These discrepancies between studies might be explained by the heterogeneity of the depressive episodes, medication status, and differences in the emotional paradigms and analysis methods.

Nonetheless, the shift in the activation of the S/SM network observed in patients when having anticipatory information might be explained by an enhanced emotional conflict when observing positive stimuli, due to an incongruence between the stimuli valence and patients' persistent depressed mood. Dorsal ACC, a core region of the salience network, plays a crucial role in conflict monitoring (Stevens et al., 2011). In fact, previous fMRI studies reported an hyperactivation of the dorsal ACC during reward anticipation in depression, supporting our hypothesis (Gorka et al., 2014; Knutson et al., 2008). Moreover, a decrease in the S/SM network is observed when patients observe mood-congruent stimuli (i.e., negative stimuli) after anticipatory cues, suggesting no emotional conflict and further supporting our hypothesis.

To better understand how this S/SM network interacted with other brain regions PPI analyses were performed, which showed enhanced FC between the S/SM network and the left amygdala in MDD patients when processing negative uncued stimuli. This pattern of FC has been extensively reported in the literature during distinct emotional paradigms and at rest in depressed patients (Ho et al., 2014; Jenkins et al., 2017; Young et al., 2016). In fact, amygdala is hyper-responsive to negative stimuli in depression (Hamilton et al., 2012), displaying a more intense and long-lasting response in patients than controls (Drevets et al., 2008; Siegle et al., 2002). Given that this subcortical structure is interconnected with multiple cortical structures, such as nodes of salience network (Stein et al., 2007), its persistent hyper-responsiveness potenti-
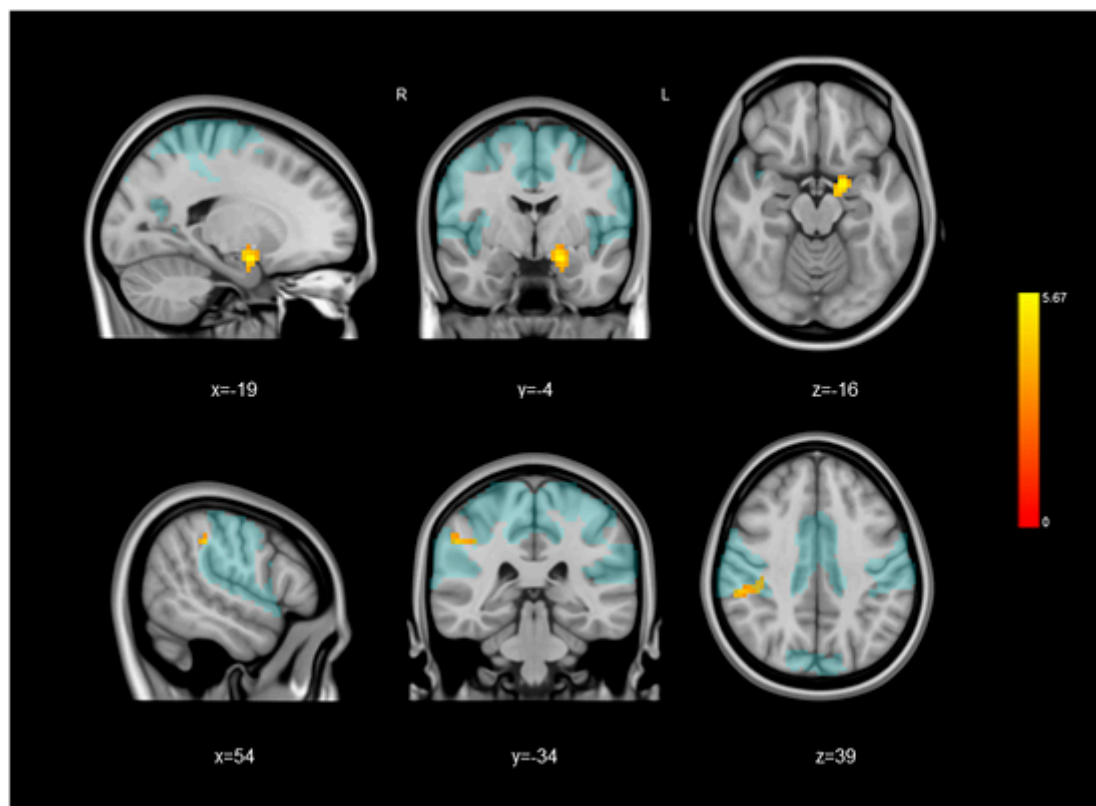
Fig. 3. Statistically significant increased functional connectivity between the S/SM network and the left amygdala and the right inferior parietal lobule in patients compared to controls when observing negative vs. neutral uncued pictures. In light blue is represented the S/SM network and in red-yellow the brain regions with an increased functional connectivity. MNI coordinates are represented by x, y, and z. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

ates bottom-up signals to these cortical regions (Disner et al., 2011; Hamilton et al., 2012). Although we did not find statistically significant results in the limbic network, these findings support the previous literature on its abnormal neural mechanisms in depression (Disner et al., 2011; Drevets et al., 2008; Hamilton et al., 2012). Moreover, when processing negative uncued stimuli, patients showed an increased FC between the S/SM network and the right IPL, a prominent node of the fronto-parietal central executive network (CEN). The CEN could be excessively recruited by the salience network in patients with MDD when processing external salient stimuli (Jiang et al., 2017; Li et al., 2021; Luo et al., 2021), leading to an excessive attention towards emotional stimuli. Altogether, these findings reflect the negative biases typically associated with depression.

Finally, our exploratory analyses revealed a negative correlation between the DMN activation for positive (vs. neutral) uncued pictures and suicidal ideation. This brain network has been implicated in self-referential mental processes (Buckner et al., 2008). Previous studies reported a disruption of DMN in both suicidal ideation and behaviors at rest and during task fMRI (Du et al., 2017; Malhi et al., 2019; Ordaz et al., 2018). Even though our findings should be considered preliminary and interpreted with caution, future studies are needed to better understand the role of this network in the suicide path in depression.

5. Limitations

Despite the promising findings of this study, several limitations must be considered. Our sample size was modest, due to the difficulty of recruiting participants meeting the strict inclusion and exclusion criteria of this study. Nevertheless, a sample of drug-naïve patients allows to confidently exclude the confounding effects of medication and it is relatively scarce in the literature, which is a major strength of this study.

Moreover, the network defined as S/SM network included motor and parietal regions, not typically included as part of the salience network. However, the association between the S/SM network and the amygdala gives us confidence on the reliability of this network, due to their consistently described association both in clinical and healthy populations (Carballedo et al., 2011; Pannekoek et al., 2014; Roy et al., 2009; Touroutoglou et al., 2014; Young et al., 2016). Thus, these findings should be considered preliminary and await further replication. Future studies should address these limitations, and further explore how these networks are modulated after antidepressant treatment or other interventions, given that previous studies have shown that antidepressants can normalize brain activity during emotional processing (Delaveau et al., 2011; Wessa and Lois, 2015).

6. Conclusion

S/SM network activation is shifted by anticipatory cues during emotional processing in drug-naïve depressed patients. This network also showed an increased FC with the left amygdala and the right IPL during the observation of negative (vs. neutral) pictures. Although these findings should be interpreted considering the limitations highlighted above, the present study brings new insights into the field by using a data-driven network approach with a sample of drug-naïve depressed patients.

Authors' contributions

JMB and NS conceived the study. JMB recruited the participants. RV and CPN organized the database, scheduled, and performed the assessments of the participants. JR, AC, RM, SF, and PSM performed the MRI acquisitions. RV and MPP performed the MRI data pre-processing and

data analyses. RV wrote the first draft of the manuscript. All the authors contributed for the following and final versions of the manuscript.

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgements

The authors would like to thank the study participants and the Clinical Academic Center – Braga staff for their help and availability during the data collection period.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2022.09.165.

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