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Self-other referential neural processing in social anxiety disorder and major depressive disorder

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ABSTRACT

Background: Social anxiety disorder (SAD) and major depressive disorder (MDD) are highly comorbid and share impairments in self-referential and social processing. Many naturalistic judgements activate these processes concurrently, which can be referred to as “self-other referential processing”. We sought to examine its neural correlates in young people with SAD and MDD using a novel experimental task.

Methods: Fifty six young people aged 16 to 25 with diagnoses of SAD and/or MDD (15 with SAD [M = 20.3 years, 60% female], 17 with MDD [M = 19.8 years, 53% female], 24 with comorbid SAD and MDD [M = 19.8 years, 67% female]) and 76 age and gender-matched healthy controls (HCs; M = 20.7 years, 66% female) completed a novel self-other referential processing fMRI task that involved rating how much one related to emotional faces in active conditions and judging how far apart each person’s eyes were in control conditions.

Results: Participants with SAD had more and those with MDD had less activity in social cognitive areas than HCs when processing social information across all conditions and emotion types. Participants with comorbid SAD-MDD exhibited a distinct pattern of neural activity to patients with single diagnoses. Across the whole sample, the activation of reward system areas (the medial orbitofrontal cortex and caudate) in response to increasing relatedness correlated positively with a dimensional measure of social anxiety.

Conclusions: Young people with SAD, MDD and comorbid SAD-MDD showed deficits in social processing, but they were not specifically related to self-other referential processing. Dimensional social anxiety symptoms were correlated with reward system activation, suggesting that such symptoms are associated with an overestimation of the hedonic value of social stimuli. These novel findings have implications for our understanding of the neural correlates of SAD and MDD, suggesting that alterations in social processing and reward functioning underlie the impairments in self and social processing that characterize both disorders.

1. Introduction

Disturbances of self and social functioning are important characteristics of mood and anxiety disorders (American Psychiatric Association, 2013), including social anxiety disorder (SAD) and major depressive disorder (MDD). People with SAD suffer from a persistent fear of social or performance situations, continually worrying that they will embarrass or humiliate themselves in front of others. These symptoms include impairments in self-functioning, where people with SAD believe that their traits and behaviours are embarrassing. SAD is also characterized by deficits in social cognition, with sufferers assuming that others are hostile and will judge them. People with MDD also experience

impairments in self-concept, suffering reduced self-esteem and confidence; and in their relationship with others, believing that they are unworthy of being liked or having excessive feelings of guilt (American Psychiatric Association, 2013). The two conditions are highly comorbid, with about half of those with SAD having a co-occurring diagnosis of MDD, while about a third of people with MDD are also diagnosed with SAD (Koyuncu et al., 2019). People with comorbid diagnoses of SAD and MDD have poorer outcomes than those with either condition alone (Dalrymple and Zimmerman, 2007; Koyuncu et al., 2014, 2019). How the overlap in self and social functioning impairments between the disorders relates to their comorbidity remains unclear. There is some evidence to suggest that, at a behavioural and a neural level, the two

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processes may have an additive or overlapping effect, particularly when integrated. This is evident both in studies demonstrating shared neural architecture, which will be discussed in more depth below, and also in those proposing shared cognitive processes (Mak et al., 2017; Northoff and Bermpohl, 2004; Northoff et al., 2006; Qin and Northoff, 2011; van der Meer et al., 2010). It has been argued that self- and other-referential processes are inextricably linked, with one being necessary for the other (Forgas and Williams, 2002; Northoff, 2013). Our sense of self is informed by the social information we collect about ourselves from our environment (Mead and Morris, 1934). Similarly, we model the experiences of others using our internal model of ourselves, by imagining how we would think and behave in their position (Forgas and Williams, 2002; Molnar-Szakacs and Uddin, 2013; Uddin et al., 2007). Given this, it is clear that self and social processes are frequently integrated in real-life situations. Better understanding how this integrated form of processing is impaired in SAD and MDD will give us a deeper understanding of both disorders.

To date, functional magnetic resonance imaging (fMRI) studies have largely investigated self and other-referential processing separately. In healthy individuals, studies have shown that both self- and other-referential processing are associated with activation of the default mode network (DMN), which includes cortical midline structures such as the extended medial prefrontal cortex (MPFC) and posterior cingulate cortex (PCC), as well as functionally connected lateral posterior areas, including the inferior parietal lobule (IPL) and temporoparietal junction (TPJ) (Mak et al., 2017; Northoff and Bermpohl, 2004; Northoff et al., 2006; Qin and Northoff, 2011; van der Meer et al., 2010). Studies investigating other-referential processing additionally implicate brain regions that commonly underlie social cognition (here referred to as the social cognition system or SCS). These include the inferior frontal gyrus, anterior insula, parietal regions (including the IPL), ventral premotor and supplementary motor cortices (Molnar-Szakacs and Uddin, 2013; Uddin et al., 2007). Some studies have also noted considerable recruitment of the reward system during self-referential processing, particularly when participants saw stimuli as increasingly self-related (Northoff and Hayes, 2011). The reward system is a distributed network of brain areas that are involved in processing rewarding stimuli, which are objects or goals that individuals deem valuable and so work to acquire, via allocation of time, energy or effort (Arias-Carrión et al., 2010; Northoff and Hayes, 2011; Northoff et al., 2009; Phan et al., 2004). This network includes the vMPFC, orbitofrontal cortex, striatum, substantia nigra and ventral tegmental area (Arias-Carrión et al., 2010; Fettes et al., 2017).

Compared to healthy people, SAD and MDD patients exhibit impaired neural activity when engaging in self and social processing. Studies have shown that when processing social information the two disorders exhibited contrasting patterns of hyper- and hypoactivation throughout the DMN and SCS (Beesdo et al., 2009; MacNamara et al., 2017). Patients with both disorders showed hyperactivation of the DMN during self-referential processing (Abraham et al., 2013; Blair et al., 2008, 2011; Lou et al., 2019; Nejad et al., 2013; Sarsam et al., 2013). A study from our group showed that when comorbid the disorders had an additive effect, increasing aberrant MPFC-PCC connectivity (Davey et al., 2017). Few studies have specifically investigated the integration of self and social processes, which we have termed “self-other referential processing”. Instead, they have focused on related processes such as self-referential criticism delivered by others, emotional memory and inducing anxiety in social situations (Burklund et al., 2017; Heitmann et al., 2014; Holt et al., 2016; Kessler et al., 2011; Komulainen et al., 2018; Nakao et al., 2011; Pujol et al., 2013; Yoon et al., 2016; Ziv et al., 2013). While not directly assessing the neural correlates of self-other referential processing, these studies found increased activity in SAD compared to healthy participants in key regions of the DMN and SCS when they thought about themselves in relation to others (Burklund et al., 2017; Heitmann et al., 2014; Holt et al., 2016; Kessler et al., 2011; Komulainen et al., 2018; Nakao et al., 2011; Pujol et al., 2013; Yoon et al., 2016; Ziv et al., 2013). In MDD, two similar studies reported no

difference in neural activity between MDD patients and healthy controls during contrasts that isolated self-other referential processing, despite finding other group differences (Holt et al., 2016; Komulainen et al., 2018). A third study, however, found that, like in SAD, individuals with MDD showed more activity in the DMN and SCS compared with HCs when thinking about themselves in relation to others (Kessler et al., 2011).

In the current study we aimed to extend previous work by investigating the neural correlates of self-other referential processing in young people with SAD, MDD and comorbid SAD-MDD. Given the centrality of impairments in self and social processing in both SAD and MDD, the study was designed to determine whether neural deficits related to integrated self-other referential processing were distinct or shared between the disorders. Establishing whether comorbid SAD-MDD showed additive effects of disrupted self-other referential processing was also of interest. In order to improve upon existing studies we employed a task that deliberately integrated self and social processing in a judgement with arguably higher ecological validity, as it is often used in everyday life. This judgement of self-other relatedness should have involved first mentally modelling the self, then an unknown other, and comparing the two. As such, our study additionally provides novel evidence of the neural correlates of self-other relatedness and how these differ between patients and HCs. We investigated self-other referential processing in largely treatment-naïve young people because it allowed us to examine the influence of comorbidity directly and without the confounding factors of prior treatments. Based on previous research, we hypothesised that the DMN and SCS would show increased activation during self-other referential processing in patients when compared to HCs. We also expected this activity to be modulated by differences in relatedness and emotional valence, and that these effects would be stronger in patients compared to HCs. Finally, we hypothesised that a dimensional measure of social anxiety symptom severity would correlate with neural activity during self-other referential processing such that increasing activity would be associated with increasing psychopathology.

2. Methods

2.1. Participants

The study was approved by the University of Melbourne Human Research Ethics Committee and was carried out in accordance with the Declaration of Helsinki. All participants provided their informed consent to participate in the study. Seventy-eight unmedicated patients with SAD and/or MDD were recruited at *headspace* centers and the University of Melbourne Psychology Clinic in Melbourne, Australia. *headspace* is a national youth mental health foundation funded by the Australian Government Department of Health. The University of Melbourne Psychology Clinic is a university training clinic for postgraduate psychology students. Patients were between the ages of 16 and 25 and had a diagnosis of SAD, a diagnosis of MDD or comorbid diagnoses of SAD and MDD as assessed with the Structured Clinical Interview for DSM-5 Disorders, Research Version (SCID-5-RV) (First et al., 2015), without current or past diagnosis of a psychotic or bipolar disorder. The SAD group could not meet the cut off for MDD of moderate or greater severity, as indicated by a score of 20 or more on the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979). Similarly, the MDD group could not meet criteria for SAD of moderate or greater severity, as indicated by a score on the Leibowitz Social Anxiety Scale (LSAS) (Liebowitz, 1987) of 66 or greater. We allowed mild versions of the comorbid condition in each group because of how common the diagnoses were. Of the patients, 21 were categorized as being in the SAD group, 24 in the MDD group, and 33 in the comorbid group. All patients met the following eligibility criteria: (i) competent spoken English (assessed in a phone interview), (ii) no current treatment with psychoactive medications, including antidepressant, antipsychotic, mood-stabilizing or sedative-hypnotic medications, (iii) no dependence on

alcohol or other drugs, as determined by the World Health Organization Alcohol, Smoking and Substance Involvement Screening Test Version 3.0 (WHO ASSIST V3.0) (WHO ASSIST Working Group, 2002), (iv) no major neural abnormalities as indicated by the MRI, and (v) no further contraindications to MRI.

Of the SAD participants, three were subsequently excluded due to excessive head motion during fMRI (see the Image Preprocessing section for more details) and three were unable to complete the scan. Six MDD participants were excluded due to excessive head motion, while one was excluded because of an incidental finding. Five comorbid participants were excluded due to head motion, two to scan incompleteness, and one to an incidental finding. This left final samples of 15 SAD participants (60.0% female; $M = 20.27$ years old, $SD = 2.63$ years), 17 MDD participants (52.9% female; $M = 19.76$ years old, $SD = 2.41$ years) and 24 comorbid participants (66.7% female; $M = 19.79$ years old, $SD = 2.45$ years).

The clinical groups were compared to 122 healthy young people. They were recruited to the study via an online classified advertisement website (“Gumtree”), electronic student noticeboards at The University of Melbourne, and by word of mouth. In addition to the general eligibility criteria listed above, healthy control participants also had to have no current or past diagnosis of a mental illness based on participant history and the SCID-5-RV. Twenty-four HC participants were excluded; 21 due to excessive head motion, one following a technical failure during fMRI, and two for incidental findings. A total of 98 HC participants (67.35% female; $M = 21.49$ years old, $SD = 2.20$ years) were then matched on age to the patient sample, leaving a final total of 76 HC participants (65.8% female; $M = 20.66$ years old, $SD = 1.76$ years). See Table 1 for final group demographic and clinical characteristics.

2.2. fMRI task

We developed a novel ‘social judgement task’ that sought to evoke integrated self-other referential appraisals by having participants rate how much they felt they would relate to a person based on a picture of their face, featuring one of three facial expressions (Fig. 1). Participants were presented with a series of people’s faces and were asked two possible questions about them. First, they were asked how much they related to the person based on their appearance. To answer this question, they were instructed to think about the potential qualities and characteristics of the person in relation to their own qualities and characteristics, and whether they would be similar or relatable. We suggested that participants imagined encountering the person in a common setting (such as at a party, in class, or on the bus), and whether they felt the person would be someone they would like to talk to. Participants were told that, after viewing each face for a short period, they would need to respond to the question using a button box on a three-point scale, indicating that they (i) did not relate to that person at all, (ii) related to them somewhat, or (iii) related to the person very much. For control conditions, participants were asked to judge how far apart people’s eyes were. They could answer that the eyes were (i) very close together, (ii) somewhat close together, or (iii) far apart.

The task comprised six conditions (three active and three control). All included an initial instruction followed by a face stimulus, which either displayed an angry, happy or neutral expression. The relatedness

question was represented by the word “relate”, which preceded each stimulus in the active conditions, while the eye distance question was indicated by the word “eyes”, which preceded each stimulus in the control conditions. The six conditions were therefore: ‘happy relate’ (relate question with a happy face), ‘angry relate’ (relate question with an angry face), ‘neutral relate’ (relate question with a neutral face), and ‘happy eyes’ (eyes question with a happy face), ‘angry eyes’ (eyes question with an angry face), and ‘neutral eyes’ (eyes question with a neutral face).

In total, the task comprised 72 events. The instruction period interval for each event was 500 ms and involved the presentation of the word “eyes” or “relate”, rendered in blue or green lowercase text, respectively, on a black background. The instruction was followed by an emotional face stimulus with an interval of 6000 ms, with an interval of 2000–10,000 ms before the presentation of the next face. All faces were taken from the Radboud Faces Database (Langner et al., 2010). There were 18 female and 18 male faces included in the task, comprising a total of 36 faces. Twelve faces (six male and six female) were assigned to each of the three emotion types, with each set of faces being displayed twice: once in a relate condition and once in an eyes condition. Emotional faces were pseudo-randomized, with an established order of presentation of each condition, but with randomization of the particular face shown. Event timing and sequencing was optimized using optseq2 (<https://surfer.nmr.mgh.harvard.edu/optseq/>). Three versions of the task were generated to counterbalance the set of faces displayed for each emotion type. It was presented using Paradigm software (<http://www.paradigmexperiments.com>) on a Dell computer via MRI-compatible high-resolution goggles (VisuaStim Digital System, Resonance Technology Inc., Northridge, CA). Participants’ responses were registered with a fORP curved 4-button response box (Cambridge Research Systems Ltd.).

2.3. Image acquisition

A 3 T General Electric Discovery MR750 system equipped with an eight-channel phased-array head coil was used in combination with ASSET parallel imaging. The functional sequence consisted of a single-shot gradient-recalled EPI sequence in the steady state (repetition time, 2 s; echo time, 35 ms; and pulse angle, 90°) in a 23-cm field-of-view, with a 64×64 -pixel matrix and a slice thickness of 3.5 mm (no gap). Thirty-six interleaved slices were acquired parallel to the anterior–posterior commissure line with a 20° anterior tilt to better cover ventral prefrontal cortical brain regions. The total sequence time was 12 min 12 s, corresponding to 362 whole-brain echo-planar imaging volumes. To assist with noise reduction and head immobility, all participants were fitted with insert-ear protection and had their heads supported with foam-padding inserts.

2.4. Image pre-processing

Imaging data was transferred to a Unix-based platform that ran MATLAB Version 9.3 (The MathWorks Inc., Natick, USA) and Statistical Parametric Mapping (SPM) Version 12 (Wellcome Trust Centre for Neuroimaging, UK). Motion correction was performed by realigning each participant’s time series to the first image using least-squares

Table 1
Demographic and clinical characteristics of the participants.

Characteristic(mean ± SD)	SAD	MDD	Comorbid	HC	Chi Square or Welch’s F	P
Female (N, %)	60%	52.9%	66.7%	67.35%	$\chi^2 = 2.06$	0.914
Age (years)	20.27 ± 2.63	19.76 ± 2.41	19.79 ± 2.45	21.49 ± 2.20	1.36	0.272
WTAR Score (IQ)	36.20 ± 8.86	40.59 ± 6.35	37.96 ± 9.00	39.41 ± 4.87	1.00	0.408
Years of education	13.63 ± 1.91	13.53 ± 1.76	14.27 ± 2.27	15.28 ± 1.80	6.73	.001 ^a
LSAS Score	78.87 ± 21.02	51.47 ± 20.31	86.88 ± 24.83	21.55 ± 14.33	79.09	<.0001 ^a
MADRS Score	16.40 ± 7.85	25.47 ± 7.20	27.96 ± 8.07	2.30 ± 3.25	30.37	<.0001 ^a

^a Statistically significant, $P < .05$.

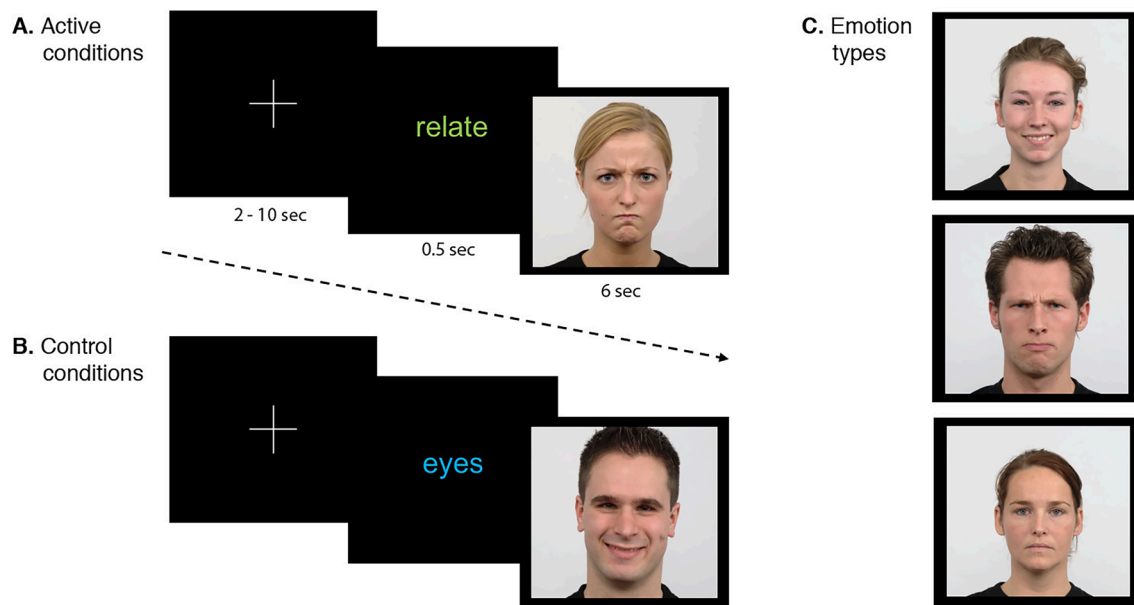


Fig. 1. Experimental paradigm. Fixation cross followed by a question prompt and an emotional face stimulus in the active (relate) (A) and control (eyes) (B) conditions. Examples of the three emotion types available in both conditions are in (C); happy, angry and neutral.

minimization and a six-parameter rigid body transformation. Motion fingerprint (SPM toolbox) (Wilke, 2012) was used to quantify participant head motion. Participants were excluded if movement exceeded 2 mm mean total displacement or 2.5 mm maximum scan-to-scan displacement. After slice-timing correction, the realigned functional images were then spatially normalized to the International Consortium for Brain Mapping template, resliced to 2 mm isotropic resolution, and smoothed with a 6 mm fullwidth-at-half-maximum Gaussian filter.

2.5. Subject-level fMRI analysis

Two subject-level general linear models were constructed. The first (*Model 1*) separated the events into the six conditions mentioned above. With this model we intended to broadly examine brain responses to the task, as well as their modulation by the affective content of facial expressions. The second (*Model 2*) grouped events during the relate conditions according to participants' 'relatedness' responses ("not at all", "somewhat", or "very much"), while events from the eyes conditions were grouped according to distance responses ("very close", "somewhat close", "far apart"). *Model 2* was intended to examine the degree to which brain activity was directly modulated by participants' ratings of self-relatedness. *Model 2* was estimated in a reduced number of participants, as not all participants provided responses across all conditions: 14 SAD (64.3% female, $M = 20.14$ years old, $SD = 2.68$ years), 13 MDD (46.2% female, $M = 19.46$ years old, $SD = 2.40$ years), 16 comorbid (62.5% female, $M = 19.19$ years old, $SD = 2.29$ years) and 71 HC participants (66.2% female; $M = 20.69$ years old, $SD = 1.66$ years).

Primary regressors specifying the onset and duration of each event for both models were entered for each participant. The events in the models were convolved with a canonical hemodynamic response function. The rest-fixation epochs served as the implicit baseline. A high-pass filter (1/128 s) accounted for low-frequency noise, while temporal autocorrelations were estimated using a first-order autoregressive (AR1) model. Regression coefficient estimates (betas) were calculated using a Restricted Maximum Likelihood approach and primary contrast images were estimated for each participant: all relate > rest contrasts for each group (e.g. relate happy > rest, eyes angry > rest) (*Model 1*), all response type > rest contrasts (e.g. relate very much > rest; eyes far apart > rest) and the relate very much > relate not at all contrast (*Model 2*).

2.6. Group-level fMRI analysis

Group-level GLM analyses were performed using the summary statistics approach to random-effects analyses. Subject-level contrast images for *Model 1* were carried forward to the second level, where a full factorial was estimated. This model had four factors: SAD, MDD, condition and emotion. For *Model 2*, a full factorial was created with a similar factor structure: SAD, MDD, condition and response type (responding with a 1, 2 or 3 on the button box). Main effects and interactions were examined for both models, with post-hoc pairwise comparisons estimated where significant effects were found. All main effect and interaction analyses were restricted to an inclusive grey matter mask, created in the WFU PickAtlas SPM toolbox (Wake Forest University School of Medicine) and thresholded at small volume corrected (SVC) false discovery rate (FDR) ($p < .05$, $K_E = 10$ voxels), with an entry threshold of $p < .001$ uncorrected. Similar to previous studies, this mask was used to exclude white matter and non-brain areas from analysis, thereby reducing noise and increasing the likelihood of correctly detecting a significant result (van Buuren et al., 2020). Post-hoc pairwise comparisons were masked by the resulting map of the relevant main effect or interaction and thresholded at SVC-FDR ($p < .05$, $K_E = 10$ voxels), with an entry threshold of $p < .001$ uncorrected.

Whole brain analyses were also carried out. For these, main effect and interaction analyses were thresholded at $p < .05$, $K_E = 10$ voxels and corrected for multiple comparisons using FDR. Subsequent post-hoc pairwise comparisons were masked by the resulting map of the relevant main effect or interaction and thresholded at SVC-FDR ($p < .05$, $K_E = 10$ voxels), with an entry threshold of $p < .001$ uncorrected.

2.7. Task performance associations

We examined associations between behavioral and brain measures of task performance with trait measures of social anxiety (LSAS) and depression (MADRS). Associations between task behavioral performance (relatedness ratings) and trait measures were estimated by Pearson's correlation in SPSS Statistics 24 (IBM Corp, USA). Any missed responses were imputed. Imputed item values were based on the mode of responses for the question across all participants within the group in question, while unit imputation of the total score on a measure was based on the mean of total scores within the group and rounded to the

closest integer that represented a real score. All results were also replicated by listwise deletion to handle missingness. The association between brain activity and LSAS scores was estimated by specifying the LSAS as a covariate within a one sample *t*-test of the very much > not at all (*Model 2*) contrast. This analysis was restricted to an inclusive mask of the self-relatedness very much > not at all group result, thresholded at SVC-FDR ($p < .05$, $K_E = 10$ voxels), with an entry threshold of $p < .001$ uncorrected. The group result itself was restricted to the inclusive grey matter mask and thresholded at SVC-FDR ($p < .05$, $K_E = 10$ voxels), with an entry threshold of $p < .001$ uncorrected.

3. Results

3.1. Behavioral data analysis

One-way Welch's ANOVAs and a chi square test showed that the groups did not differ on age, sex or intelligence (Table 1). SAD and MDD patients had engaged in fewer years of education than HCs (see Supplementary Table 1 for post-hoc pairwise comparisons). There were also significant differences between the groups in LSAS and MADRS scores. All patient groups had significantly higher LSAS scores than HCs. SAD and comorbid participants had significantly higher scores than MDD patients, and did not differ from each other. The MADRS produced similar results, with patients having significantly higher scores than HCs. MDD and comorbid participants had significantly higher scores than SAD patients, and did not differ from each other.

A repeated measures ANOVA of reaction time revealed significant two-way interactions between condition and group, and between condition and emotion (Supplementary Tables 2-4). Subsequent simple main effects analyses showed that within the relate conditions HCs responded more slowly than SAD and MDD participants. Comorbid participants took longer to respond to faces in the relate conditions than in the eyes conditions. All participants responded to neutral faces significantly more slowly in the relate than the eyes conditions. There was also a significant simple main effect of emotion within both the relate and eyes conditions. Bonferroni corrected post-hoc pairwise comparisons revealed that participants reacted more slowly to neutral than happy faces in the relate conditions. In the eyes conditions participants responded more slowly to happy and angry faces than neutral faces.

A repeated measures ANOVA of participant relatedness ratings revealed a significant main effect of emotion type, along with a significant interaction between emotion type and group (Supplementary Tables 5-7). There was a simple main effect of group within the happy emotional category. Games-Howell post-hoc pairwise comparisons showed that HCs related significantly more to happy faces than MDD and comorbid participants. There was a significant main effect of emotion within both the SAD and comorbid groups, such that they related more to neutral than angry faces. There was also a main effect of emotion within the HC group. Pairwise comparisons showed significant differences between ratings of all emotions, with HCs relating the most to happy, then neutral and finally angry faces. MDD participants related equally to all emotion types.

Relatedness ratings of happy faces were also significantly negatively correlated with MADRS scores ($r = -0.479$, $p < .0001$) and LSAS scores ($r = -0.456$, $p < .0001$) across the whole group. Relatedness ratings of angry and neutral faces did not correlate with either measure of symptom severity.

3.2. fMRI group analysis

3.2.1. Model 1: Self-other referential judgement

There were main effects of both condition and emotion. The simple main effect of relate > eyes showed widespread significant activation of brain regions routinely implicated in self- and other-referential processing, as well as general emotional-affective responding. This pattern

of activation involved the MPFC, including both its ventral and dorsal regions, and extended to the rostral anterior cingulate cortex. Extensive activation of the posterior medial cortex was also observed, spanning the posterior cingulate and retrosplenial cortex, and the cuneus-precuneus. Other prominently activated areas included the middle temporal gyrus, TPJ and temporal pole; hippocampus-amygdala; frontal operculum-inferior frontal gyrus; striatum and medial thalamus (Fig. 2 and Supplementary Table 8). The main effect of emotion corresponded to significant activation of temporal, visual and face processing areas. In addition, activation of key components of the DMN and SCS were observed, including the inferior frontal gyrus, supramarginal and angular gyri, and ventral MPFC (Supplementary Table 9 and Supplementary Figure 1).

There were main effects of MDD and SAD, as well as an interaction between these factors. The simple main effect of MDD revealed that these patients had significantly reduced activation of the precuneus, supramarginal gyrus, pre- and post-central gyri and areas related to vision and face processing across all conditions, compared to those without MDD (including both HCs and SAD participants) (Supplementary Table 10 and Supplementary Figure 2). As a simple main effect, patients with SAD demonstrated significantly greater activation of lateral frontal areas, pre- and post-central gyri, cerebellum and face processing areas than those without SAD (Supplementary Table 11 and Supplementary Figure 3).

The interaction of SAD and MDD revealed areas of activation that differed depending not on the basis of a participants' diagnosis of either SAD or MDD, but rather on the combination of diagnoses (i.e. their group membership: SAD, MDD, comorbid or HC). Activation associated with the interaction was seen in SCS and DMN areas, including the precuneus, supramarginal gyrus, precentral gyrus and visual regions (Fig. 3 and Supplementary Table 12). Post-hoc tests regarding the interaction of SAD and MDD revealed areas of differential activation between the groups (Supplementary Table 13). The significant clusters overlap those seen in the interaction of SAD and MDD. There was significantly greater activation of the precentral gyrus in comorbid patients than all other groups, and in the cuneus compared to patients with SAD. Participants in the SAD group displayed greater activation in the inferior occipital gyrus than comorbid participants and HCs. HCs showed more activity in the precentral and supramarginal gyri than MDD participants; and in the cuneus when compared to the SAD group. There were no interactions between diagnosis and condition.

3.2.2. Model 2: Modulation by degree of self-relatedness

There was an interaction between response type and condition, with significant regions throughout reward areas (anterior orbital gyrus, medial orbital gyrus, thalamus, caudate), as well as the dorsal MPFC, angular and supramarginal gyri, precuneus, PCC, lateral frontal regions, motor areas and the superior parietal lobule (Fig. 4 and Supplementary Table 14).

A post-hoc pairwise comparison showed that in the relate condition greater relatedness (very much > not at all contrast) was associated with greater activation of reward areas, extending through the basal ganglia (nucleus accumbens and caudate), thalamus, anterior insula, ACC, orbitofrontal cortex and subcallosal area. There was also significant activation of the dorsal MPFC, the inferior and middle frontal gyri, the supplementary motor cortex, and inferior temporal gyrus (Fig. 5 and Supplementary Table 15). There was no interaction between response type and diagnosis.

3.2.3. Correlations with behavioral measures

We identified a significant correlation between dimensional social anxiety and brain activation in the very much > not at all contrast. Scores on the LSAS correlated positively with activation of the bilateral caudate and left medial orbital gyrus (Fig. 6 and Supplementary Table 16).

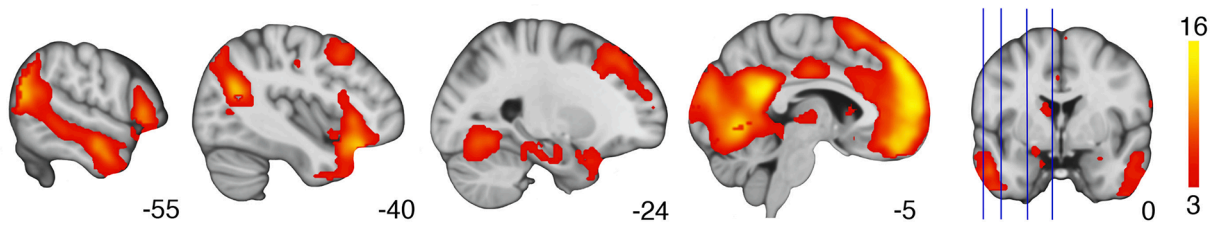


Fig. 2. Activation map representing self-other referential processing (simple main effect of condition: relate > eyes). Activation thresholded at SVC-FDR $P < .05$, $K_E = 10$ within a mask of the main effect of condition, entry threshold of $P_{Uncorrected} < 0.001$. Left = left.

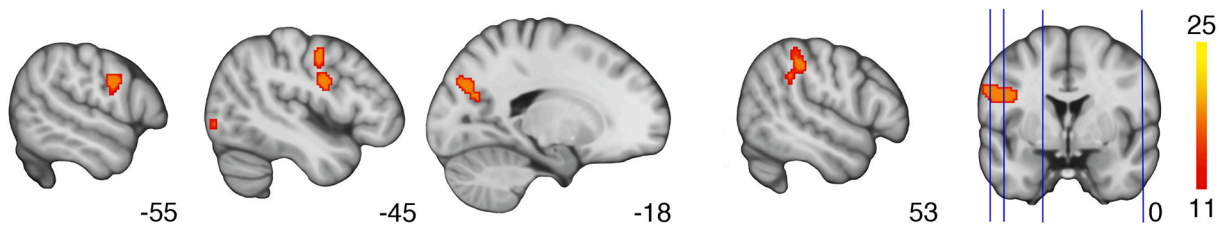


Fig. 3. Activation map showing the interaction of SAD and MDD. Activation thresholded at SVC-FDR $P < .05$, $K_E = 10$ within a grey matter mask, entry threshold of $P_{Uncorrected} < 0.001$. Left = left.

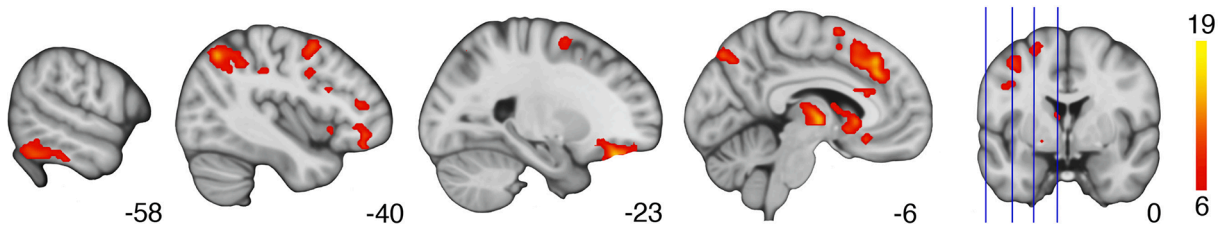


Fig. 4. Activation map showing the interaction of response type and condition. Activation thresholded at SVC-FDR $P < .05$, $K_E = 10$ within a grey matter mask, entry threshold of $P_{Uncorrected} < 0.001$. Left = left.

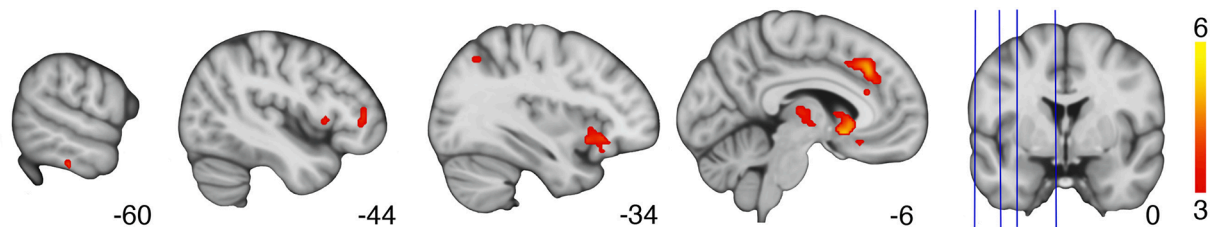


Fig. 5. Activation map representing increasing relatedness (relate very much > relate not at all). Activation thresholded at SVC-FDR $P < .05$, $K_E = 10$ within a mask of the interaction of condition and response type, entry threshold of $P_{Uncorrected} < 0.001$. Left = left.

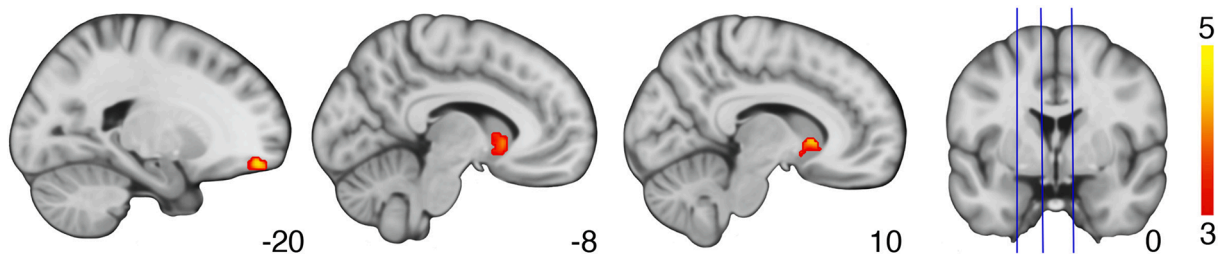


Fig. 6. Activation map representing the correlation between brain activity related to increasing relatedness (relate very much > relate not at all) and LSAS scores. Activation thresholded at SVC-FDR $P < .05$, $K_E = 10$ within a mask of the relate very much > relate not at all result, entry threshold of $P_{Uncorrected} < 0.001$. Left = left.

3.2.4. Whole brain results

Additional whole brain analyses were also carried out to confirm the SVC results. Tables outlining these results are reported in the

[Supplementary Material](#). Results for the simple main effect of condition: relate > eyes (Supplementary Table 17), main effect of emotion (Supplementary Table 18), simple main effect of MDD: no MDD > MDD

(Supplementary Table 19), simple main effect of SAD: SAD > no SAD (Supplementary Table 20), interaction of condition and response type (Supplementary Table 21) and relate very much > relate not at all (Supplementary Table 22) contrasts, along with the correlation between brain activity associated with increasing relatedness and LSAS scores (Supplementary Table 23) all closely resembled the SVC results. The interaction of SAD and MDD, however, was not significant at the whole brain level. This means that subsequent post-hoc tests could not be carried out.

4. Discussion

In this study we examined the neural correlates of integrated self and social processing in social anxiety and major depressive disorders to better understand their common impairments in the appraisal of self and others. To this end, we examined self-other referential processing in an experimental design that had participants appraise the degree to which they related to a person based on physical appearance and imagined personality. Our key finding was that, while there were no group differences specifically related to self-other referential processing, patients with SAD and MDD exhibited distinct patterns of altered activity in SCS regions across all conditions of the task. There was also a correlation between dimensional social anxiety and increased activation in reward areas when participants related to others.

4.1. Opposite and distinctive patterns of dysfunction during social processing

While there were no differences in neural activation related to self-other referential processing, each of the three patient groups exhibited a distinct pattern of brain responses during broader social processing when compared to healthy controls. Participants with SAD had greater and those with MDD had less activation of SCS and face processing regions during social processing. The comorbid SAD-MDD group showed a pattern of dysfunction unique from patients with individual diagnoses, indicating that dual diagnoses of SAD and MDD do not have an additive effect, but rather produce a distinctive set of impairments. The results for single diagnoses show that, while the two disorders share behavioral impairments in self and social processing, these deficits are associated with opposite patterns of neural activation. The involvement of SCS regions in addition to face processing areas suggests that patients show opposing deficits in higher-order social processing, which is subserved by the SCS, as well as more basic social processing, facilitated by face processing regions. The hyperactivation observed in SAD patients is well-supported by previous studies of emotional face processing and self-other referential processing that involved viewing others (Burklund et al., 2017; Gentili et al., 2016; Nakao et al., 2011; Pujol et al., 2013; Yoon et al., 2016; Ziv et al., 2013). Previous findings in MDD are quite mixed, with some studies of emotional face processing finding hyper- and others hypoactivation of similar areas to our study (Stuhrmann et al., 2011). The contrasting results in MDD and SAD patients imply that SAD is associated with increased and MDD with reduced sensitivity to relational processes. This aligns with their differential symptoms, with SAD being characterized by fear and anxiety about social situations, while MDD involves anhedonia; the loss of interest or pleasure in normal activities, including socializing (American Psychiatric Association, 2013).

4.2. Dimensional but not categorical differences in the neural correlates of increasing relatedness

Contrary to our secondary hypothesis, we observed no differences in neural activity associated with increasing relatedness between diagnostic groups. Rather, increasing relatedness was associated with activation of the DMN, SCS and reward areas across all groups. An analysis of dimensional social anxiety, on the other hand, revealed a positive

correlation between LSAS scores and activation of the caudate and medial orbitofrontal cortex, two key areas in the reward system. These regions make up part of the medial orbitofrontal cortico-striatal circuit, which encodes the subjective hedonic value of a given stimulus (Fettes et al., 2017). Our finding implies that this process, which is essential to making a judgement about relating to others in a social situation, becomes increasingly dysfunctional or sensitized with increasing levels of social anxiety. It is possible that the greater activation in this area represents hypersensitivity to the process of value assignment to social stimuli, or that social stimuli are being assigned too much or an incorrect value. This complements a previous study of reward system dysfunction in SAD, which found greater functional connectivity in patients with SAD than in HCs between these same two regions, the caudate and orbitofrontal cortex (Arnold Anteraper et al., 2014). Together, these results reveal alterations of function in the medial orbitofrontal cortico-striatal circuit that relate to the symptoms of social anxiety, including sensitivity to aversive social stimuli (American Psychiatric Association, 2013).

This idea was supported by our behavioral findings. Patients with a single or comorbid diagnosis of SAD appeared not to show the preference for happy faces seen in HCs. They only related more to neutral faces than the active threat cue present in an angry face. This suggests deficits in the normal labelling of social stimuli as positively, neutrally or negatively valenced, aligning with our findings regarding hypersensitivity in the cortico-striatal loop related to increasing social anxiety, as well as hyperactivation of the SCS during social processing. Such deficits could underlie a preoccupation with how much SAD participants relate to others that overrides the effect of facial expressions. Participants with MDD did not show any difference in relatedness between emotion types, perhaps implying that depressed individuals are not as sensitive to aversive and attractive social cues. This behavioral result is in line with the anhedonia that characterizes MDD, along with the hypoactivation seen in the SCS during social processing.

These results show that considering social anxiety as a dimensional construct is important, as it is more sensitive to deficits in reward functioning than a categorical designation. This accords with research showing that clinical social anxiety disorder is continuous with milder, subthreshold social anxiety (Ruscio, 2010).

4.3. Common activation during self-other referential processing

Contrary to our primary hypothesis, significant activation associated with overall performance of the self-other referential processing task was consistent across all four groups. As discussed above, the groups differed in neural activity, but these differences were not specific to self-other referential processing. In contrast, previous work found increased activity in response to approximations of self-other referential processing in both SAD and MDD patients when compared to HCs (Burklund et al., 2017; Heitmann et al., 2014; Kessler et al., 2011; Komulainen et al., 2018; Nakao et al., 2011; Pujol et al., 2013; Yoon et al., 2016; Ziv et al., 2013). Our conflicting finding may be due to the use of a sample of young people in the early stages of illness, compared with earlier studies that included adults (Burklund et al., 2017; Cusi et al., 2012; Gentili et al., 2016; Heitmann et al., 2014; Kessler et al., 2011; Komulainen et al., 2018; Nakao et al., 2011; Pujol et al., 2013; Yoon et al., 2016; Ziv et al., 2013). Supporting this assertion, Holt and colleagues (2016), investigated an approximation of self-other referential processing in adolescents with MDD. As in our study, they found no differences in self-other referential processing between patients and HCs. These similar results could suggest that differences in neural activity related to self-other referential processing in MDD and SAD emerge in adulthood or after medication use, which is more likely in older samples.

4.4. No emotional valence-specific group differences

While we found overall differences in neural activity relating to

emotional valence, these did not differ by group, indicating that all groups processed each emotion type similarly. This is contrary to previous research, which has demonstrated that, in comparison to HCs, people with MDD exhibit hyperactivation of emotion processing and reward regions, along with hypoactivation of emotion regulation areas in response to negatively valenced faces (Cusi et al., 2012; Turchi et al., 2017). In contrast, compared to HCs, MDD patients show hypoactivation of the amygdala and visual regions when viewing positively valenced faces (Greening et al., 2013; Henje Blom et al., 2015). SAD patients have also shown reduced amygdala activation in response to happy faces when compared to HCs (Beesdo et al., 2009) and increased activation in DMN, SCS and visual regions when viewing sad faces (Labuschagne et al., 2012). In one study, participants with comorbid SAD-MDD tended to process emotional faces similarly to those with MDD, thereby also differing from HCs (Beesdo et al., 2009). Our conflicting results may be due to the use of a more complex task that focused on self-other referential processing, rather than the passive viewing and face matching tasks employed by previous studies (Beesdo et al., 2009; Cusi et al., 2012; Greening et al., 2013; Henje Blom et al., 2015; Labuschagne et al., 2012; Turchi et al., 2017).

4.5. Limitations

Our study had some limitations. The task we used examined simple self-other referential judgements made consistently across all participants. However, judgements made in real-world situations are much more complex and individualized. Additionally, looking at self-other referential judgements that are directly relevant to an individual's psychopathology, as Kessler and colleagues (2011) did, could produce more disorder-relevant differences between groups. We also combined self- and other-referential processing in our task. This was done to enable the investigation of integrated self-other referential processing in a way that mimics real-world judgements. However, adding separate self- and other-referential conditions to the task would have allowed us to determine the extent to which the neural correlates of integrated self-other referential processing were the same as or distinct from those of separated self- and other-referential processing. Future research should consider this question. It is also possible that participants may have engaged in implicit self-other referential processing during the control task by viewing the faces of others as self-relevant. However, given the predominance of areas typically associated with self-reference (i.e., the DMN) in the simple main effect of condition (relate > eyes) contrast, it is likely that if any self-reference did occur in the other-focused control condition, it was relatively minor. The self-other referential judgements made in our task may also have been affected by the use of heuristics or biases. To maximize ecological validity, we allowed a degree of interpretation by participants when making these judgements. As such, it is possible that some participants were influenced by how much they were motivated to approach the depicted person, which might have included confounding factors such as age, racial bias and sexual attractiveness. Nevertheless, our task did replicate a commonly exercised judgement with some relevance to both SAD and MDD: social relatedness. This was validated by associations between psychopathology and performance, as well as the modulation of relatedness ratings by affective valence, which differed by group. Furthermore, this study only considered self-other referential processing in young people. While this is a key age range for the development of SAD and MDD and is therefore clinically relevant, investigating self-other referential processing more broadly in adults and children, as well as directly comparing age groups, would provide a fuller picture of the neural correlates of this potentially aberrant form of processing across the lifespan.

4.6. Conclusion

Notwithstanding these limitations, this study has been the first to demonstrate that patients with SAD, MDD and comorbid SAD-MDD

exhibit different impairments in social processing in the SCS that are stable across basic and more complex forms of social interaction. These shared, albeit opposite, impairments in social processing may explain why MDD and SAD are so likely to co-occur. However, comorbid SAD-MDD patients exhibited a unique pattern of altered activation during social processing. Our study has also shown that reward system hyperactivation is associated with increasing levels of dimensional social anxiety. This relationship may be due to the over-valuation of emotional face stimuli when participants relate to others, aligning with the hypersensitivity to social stimuli that characterizes SAD.

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CRedit authorship contribution statement

Laura Finlayson-Short: Conceptualization, Methodology, Software, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization. **Ben J. Harrison:** Conceptualization, Methodology, Formal analysis, Resources, Writing - review & editing, Supervision, Project administration, Funding acquisition. **Christopher Davey:** Conceptualization, Methodology, Formal analysis, Resources, Writing - review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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