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Interoceptive–reflective regions differentiate alexithymia traits in depersonalization disorder

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ABSTRACT

It is unclear to what degree depersonalization disorder (DPD) and alexithymia share abnormal brain mechanisms of emotional dysregulation. We compared cerebral processing of facial expressions of emotion in individuals with DPD to normal controls (NC). We presented happy and sad emotion expressions in increasing intensities from neutral (0%) through mild (50%) to intense (100%) to DPD and non-referred NC subjects in an implicit event-related fMRI design, and correlated respective brain activations with responses on the 20-item Toronto Alexithymia Scale (TAS-20) and its three subscales F1–F3. The TAS-20 predicts clinical diagnosis of DPD with a unique variance proportion of 38%. Differential regression analysis was utilized to ascertain brain regions for each alexithymia subscale. Differential regions of total alexithymia severity for happy emotion were the globus pallidus externus; for identifying feelings (TAS-20 F1 subscale), the right anterior insula; for description of feelings (F2), the right dorsal mid-anterior cingulate gyrus (BA 24); and for externally oriented cognitive style (F3), the left paracingulate gyrus (BA 32). For sad emotion, the differential region for the total TAS-20 score was the dorsal anterior cingulate gyrus (BA 24); for TAS-20 F1, the left inferior anterior insula; for TAS-20 F2, the right PCC (BA 31); and for TAS-20 F3, the right orbital gyrus (BA 10). Supporting our hypotheses, the ascertained brain regions for TAS-20 subscales subserve interoception, monitoring and reflection of internal states and emotion. The presented analyses provide evidence that alexithymia plays a substantial role in emotional dysregulation in DPD, presumably based on restrictions in interoception.

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1. Introduction

Alexithymia is a cognitive trait, which has been implicated in emotion dysregulation in a number of mental, somatoform and somatic health problems. Alexithymia is associated with reduced introspective awareness and a lack of emotional reasoning towards others and the self (Taylor, 1984). As a consequence, verbal expression of emotions and cognitive reflection of emotional processes is impaired, and this leads to a tendency to respond with unmoderated physiological arousal states towards external events (Spitzer et al., 2005). The higher autonomic reactivity is generally seen as an adverse disposition that profoundly contributes to stress-related mental and somatic disorders. A disposition towards heightened internal arousal due to increased physiological reactivity has also been demonstrated to accompany more extreme cognitive and moral tendencies (Oxley et al., 2008).

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The alexithymia syndrome was introduced as a research construct by the psychiatrist Sifneos in 1972 (Taylor, 1984), and later operationalized by Taylor and colleagues as a self-report instrument, the Toronto Alexithymia Scale (TAS-26 and TAS-20, with its factor-analytic subscales F1–F3), which is at present the most widely accepted research measure. The TAS-20 subscale F1 reflects the ability to internally discriminate and identify feelings and emotions. The TAS-20 subscale F2 consists of self-report items quantifying the capability to cognitively represent and to verbalize feelings and emotions. Finally, the F3 subscale of the TAS-20 contains self-descriptions endorsing the inclination to maintain an outward direction of attention with respect to material objects.

Recent longitudinal developmental research has also yielded evidence to support the notion that the alexithymia trait may consist of a neurodevelopmental cognitive deficit (Lemche et al., 2004), which might explain its lifetime endurance. Moreover, overlaps have recently been highlighted to exist between alexithymia and autism spectrum disorders, e.g. in the lack of emotion-related cognition, incapability of introspection, and deficits in processing reflections on significant others (Fitzgerald and Molyneux, 2004). In support of this conjecture,

a study in autism spectrum disorder found that empathy deficits observed in autism may be due to the large co-morbidity between alexithymic traits and autism (Bird et al., 2010). As has been argued, both developmental disorders share common impairments in self- and other-related mentalization. Furthermore, a view according to which alexithymia could be a neurologically driven process has recently received strong support by the replicated neuropsychological finding that alexithymia appears regularly as a consequence of traumatic brain injury (Wood and Williams, 2007; Wood et al., 2009). As is well documented, alexithymia is typically found concomitant to somatization states, depression, anxiety, cardiovascular problems and affective disorders in large population samples (Wood et al., 2009).

Emotional dysregulation is also a key feature in DPD, a syndrome often subsumed under dissociation (Sierra, 2010). Typical co-morbidities of DPD include anxiety and depression (Mula et al., 2007; Baune et al., 2010), whereas dissociative memory impairments are not regularly found when depersonalization/derealization diagnoses are present (Baker et al., 2003). Most recent studies on DPD have revealed altered social competence based on fewer self-reported cognitive empathic abilities (Lawrence et al., 2007). The empathy deficits were found to include social anxieties alongside an increased self-orientation bias, which is reminiscent of findings in alexithymia. There are bidirectional findings in DPD regarding possible emotional memory impairments. On the one hand, DPD patients showed elevated recognition for emotive words (Montagne et al., 2007), yet lacked the usual enhancement effect for emotional memories (Medford et al., 2006). This behavioral deficit corresponds to a lack of activation in the relevant cerebral regions (Medford et al., 2006). According to previous functional magnetic resonance imaging (fMRI) studies (Phillips et al., 2001), DPD patients tend to respond with increased right ventrolateral prefrontal cortex engagement towards visual emotional stimuli, instead of activating limbic regions. Recently, alexithymia level has been deemed a strong predictor of a clinical DPD diagnosis (Simeon et al., 2009). We therefore decided to investigate in greater detail the relationship between alexithymia and DPD using an experimental fMRI study. With respect to clinical alexithymia, recent findings typically suggest a strong interrelation with dissociation with regard to posttraumatic stress, emotional numbing, and alexithymia (Frewen et al., 2008). In individuals with posttraumatic stress disorder (PTSD), TAS-20 scores correlated positively with neural responses in insula, posterior cingulate cortex (PCC), and thalamus, and negatively with response in anterior cingulate cortex (ACC) (Frewen et al., 2006).

To be able to compare cerebral mechanisms of alexithymia in DPD with normal emotional functioning, we used an emotional facial expression paradigm with fast implicit visual stimulation that resembles natural social encounters. We planned to compute correlation images to ascertain brain regions associated with the TAS-20 and its subscales. Differential regression was used to identify brain regions that differ in association with questionnaire scores, which would enable us to compare both groups with respect to differential substrates of alexithymia traits. We expected to be able to find alexithymia correlations in the above regions. In particular, for normal controls, we hypothesized correlations in the (i) paracingulate/ anterior and posterior cingulate regions previously (ii) implicated in healthy controls (Berthoz et al., 2002). For DPD patients, we expected (iii) correlations in the insula, (iv) the thalamus, (v) and further regions in the pain matrix, as reported for alexithymia in clinical populations (Kano et al., 2007). For the subscales F1 and F2, specifically, we expected to find regions with interoceptive accuracy discriminating the two groups, following respective findings in normal individuals (Critchley et al., 2004): (vi) anterior insula, thalamus, operculum, and anterior cingulate. For simple correlations

of subscales F1 and F2, however, we anticipated for DPD patients regions not associated with emotional awareness (vii).

2. Experimental procedures

2.1. Participants

The Joint South London Maudsley and Institute of Psychiatry Research Ethics Committee endorsed all experimental procedures. The study was conducted in compliance with the Helsinki Declaration (World Medical Association, 1991), and normal controls (NCs) were compensated for their participation. Informed consent was signed by all subjects to the scientific use of their data. Investigated was a total sample of 21 volunteers. The nine primary-diagnosis DPD patients (mean age, 36.11 ± 7.31 SD years; education level, 2.22 ± 0.68 ; 2=junior college level) consisted of five males and four females. These patients were in treatment for DPD at the Maudsley Hospital, London, in a specialized clinic (ASD and MLP). A psychiatrist not involved in the study had independently diagnosed DPD according to DSM-IV-TR (300.6) criteria, and the clinical cut-off level of >70 on the Cambridge Depersonalization Scale (CDS) discriminative for DPD (Sierra and Berrios, 2000) was exceeded for all patients (mean score 175.77 ± 110.85). Patients were unmedicated in majority, but three of them were medicated, each with different substances (paroxetine, fluoxetine, olanzapine). Minor co-morbid dysthymic (DSM-IV-TR 300.4) and/or mild inspecific anxiety symptoms (DSM-IV-TR 300.02) were diagnosed in six patients. The DPD patients were compared to 12 normal control (NC) subjects chosen to match education, socioeconomic status, gender ratio, and general intellectual and social functioning (mean age, 27.25 ± 4.95 years; education level, 2.58 ± 0.79 ; 7 males and 5 females). All participants were right-handers according to scores on the Edinburgh Handedness Inventory (Oldfield, 1971).

2.2. Self-report questionnaire data

Clinical self-report forms were completed prior to MRI scans. All participants completed the Toronto Alexithymia Scale, 20-item version (Taylor et al., 1988, 1990), further to the CDS clinical cutoff measure for DPD (see above). The TAS factors are replicable across cultures, with well-established psychometric properties, and are a widely accepted measure of the alexithymia construct. As described above, the three subscales of the TAS, F1–F3, quantify identification feelings and emotions (F1), description of feelings and emotions (F2), and orientation to external objects (F3). A sample statement for F1 items is: "When excited, I don't know if I am sad, anxious or angry". An example of F2 statements is: "Others ask me to better explain my feelings". A representative statement in F3 is: "I like to share my opinion on things".

2.3. Implicit facial expression neuroimaging tasks

Subjects were presented with 20 facial expression stimuli at 0% (neutral)–50% (mild)–100% (intense) intensities of happy and sad emotion expressions. Separate scans were performed for happy and sad conditions. Subjects were required to determine the sex of the face in the implicit emotion recognition task. The exact paradigm is described in Appendix A linked to this article. The percentage of correct responses had been found to be the most accurate index in group comparisons with regard to type I error rates, statistical power and sensitivity for our ranges of experimental trial numbers (Rotello et al., 2008).

2.4. fMRI image acquisition and analysis

Gradient echo echoplanar imaging (EPI) data were acquired on a Neurovascular GE Signa 1.5 T system (General Electric, Milwaukee, WI, USA), equipped with 40 mT high-speed gradients at the Maudsley Hospital, London, UK. A quadrature birdcage headcoil was used for RF transmission and reception. 180 T₂*-weighted images were acquired over 6 min for each of the two tasks at each of 16 near-axial noncontiguous 7-mm-thick planes parallel to the intercommissural (anterior commissure-posterior commissure, AC-PC) line: TE 40 ms, TR 2000 ms, in-plane resolution 3.44 mm, interslice gap 0.7 mm, flip angle (FA) $\alpha 70^\circ$, matrix 64², field of view (FOV) 25 cm providing whole brain coverage. During the same session, a high-resolution EPI dataset was acquired with a gradient echo EPI pulse sequence. The structural images were acquired at 43 near-axial 3-mm-thick planes parallel to the AC-PC line: TE 73 ms, TI 180 ms, TR 16,000 ms, in-plane resolution 1.72 mm, interslice gap 0.3 mm, matrix size 128², FOV 25 cm, FA $\alpha 90^\circ$. The high resolution EPI dataset was later used to register the fMRI datasets acquired from each individual in standard stereotaxic space. The statistical software program package XBAM (www.brainmap.it) developed at the Institute of Psychiatry, was used to perform the analysis of the fMRI data. XBAM combines nonparametric permutation based resampling methods with GLM statistics, wavelet signal denoising methods, control of false-positive voxels and clusters, and reports exact significances rather than

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