



## Significant grey matter changes in a region of the orbitofrontal cortex in healthy participants predicts emotional dysregulation

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### Abstract

The traditional concept of ‘categorical’ psychiatric disorders has been challenged as many of the symptoms display a continuous distribution in the general population. We suggest that this is the case for emotional dysregulation, a key component in several categorical psychiatric disorder constructs. We used voxel-based magnetic resonance imaging morphometry in healthy human subjects ( $n = 87$ ) to study how self-reported subclinical symptoms associated with emotional dysregulation relate to brain regions assumed to be critical for emotion regulation. To measure a pure emotional dysregulation, we also corrected for subclinical symptoms of non-emotional attentional dysregulation. We show that such subclinical emotional symptoms correlate negatively with the grey matter volume of lateral orbitofrontal cortex bilaterally—a region assumed to be critical for emotion regulation and dysfunctional in psychiatric disorders involving emotional dysregulation. Importantly, this effect is mediated both by a decrease in volume associated with emotional dysregulation and an increase in volume due to non-emotional attentional dysregulation. Exploratory analysis suggests that other regions involved in emotional processing such as insula and ventral striatum also show a similar reduction in grey matter volume mirroring clinical disorders associated with emotional dysregulation. Our findings support the concept of continuous properties in psychiatric symptomatology.

**Key words:** emotional dysregulation; voxel-based morphometry; structural MRI; orbitofrontal cortex

### Introduction

Emotional dysregulation is a hallmark of several mental disorders. However, subclinical symptoms associated with emotional dysregulation also exist to a variable degree in healthy subjects. It is not known, however, whether these subclinical symptoms in healthy subjects are mechanistically related to the clinical symptoms associated with emotional dysregulation in patients. Possibly, the capacity to regulate emotions is continuously distributed in the population, where clinical disorders such as borderline personality disorder (BPD) (Lieb et al., 2004), antisocial personality disorder (APD) (Yang et al., 2009) and

emotional subtypes of attention deficit hyperactivity disorder (ADHD) (Castellanos and Tannock, 2002) belong to the end tail of this distribution. If this is the case, the previously demonstrated changes in brain morphology in subjects carrying those diagnoses should replicate as continuous changes in the same regions, correlating with measures of emotional regulation capacity in healthy subjects.

Two key regions are especially important in top-down control of emotional processing: rostral anterior cingulate cortex (rACC) (Bush et al., 2000; Petrovic et al., 2005; Etkin et al., 2006, 2011) and lateral orbitofrontal cortex (lObfc) (Petrovic et al., 2005; Eippert

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et al., 2007; Wager et al., 2008; Kanske et al., 2011; Golkar et al., 2012). rACC seems to be involved in the regulation of ongoing emotional conflicts (Bush et al., 2000; Petrovic et al., 2005; Etkin et al., 2006, 2011) and lObfc has been associated with in-depth regulation of emotional meaning, e.g. cognitive re-appraisal of emotional stimuli (Eippert et al., 2007; Wager et al., 2008; Kanske et al., 2011; Golkar et al., 2012). lObfc is also implicated in related functions such as emotional feedback, aversive error processing and emotional expectations (O'doherty et al., 2001; Petrovic et al., 2002, 2005, 2010; Kringelbach, 2005; Seymour et al., 2005). These regions interact in emotional regulation (Petrovic et al., 2010), although their exact functions are not known. It has been suggested that these regions have a critical role in psychiatric disorders displaying emotional dysregulation including BPD, APD and emotional ADHD (Castellanos and Tannock, 2002; Lieb et al., 2004; Yang and Raine, 2009; Soloff et al., 2012). Apart from lower functional activations in emotional regulation tasks (Wingenfeld et al., 2009; Yang and Raine, 2009; Schulze et al., 2011), volumetric studies have found reduced brain volume in rACC and lObfc (Soloff et al., 2008, 2012; Yang and Raine, 2009) for these disorders.

There is a complex relationship between emotional and non-emotional top-down regulation. Both regulatory systems represent separate concepts both on a psychological and neuronal level. However, tasks involving emotional regulation may also include non-emotional cognitive control processes, such as holding the task instructions on-line in working memory. For example, controlling for processes not directly regulating emotions in a cognitive re-appraisal task of emotional stimuli task will more reliably activate lObfc than when not controlling for those factors (Wager et al., 2008; Golkar et al., 2012). In contrast, tasks where general attentional processes are not controlled for involve more robust activations of dorsolateral prefrontal cortex (dlPFC) (Wager et al., 2008; Golkar et al., 2012). Moreover, attentional tasks (Simpson et al., 2000) and resting state studies (Fox et al., 2005; Fransson, 2005) have indicated that rACC and caudal ACC (cACC) may belong to mutually inhibitory networks. Thus, in order to study the specific emotional regulation component the assessment must control for the non-emotional attentional processes (Wager et al., 2008; Golkar et al., 2012). We have found no previous account of such an approach in functional and structural imaging studies of specific psychiatric disorders.

We hypothesized that the biological basis for the capacity of emotional regulation in healthy subjects is mirrored in a structural variability of rACC and lObfc as has previously been indicated for clinical states involving emotional dysregulation (Soloff et al., 2008, 2012; Yang and Raine, 2009). To probe this hypothesis, we examined the relationship between structural variability in grey matter volume (GMV) of rACC and lObfc indicated by voxel-based magnetic resonance imaging (MRI) morphometry (voxel-based morphometry; VBM), and behaviour measured by rated subclinical symptoms associated with emotional dysregulation.

## Materials and methods

### Subjects and ethics

The subjects ( $n = 87$ ; mean age = 39.2, s.d. = 14.9; male:  $n = 40$ , female:  $n = 47$ ) were enrolled as a part of a project studying affective disorders (Jakobsson et al., 2012). The study was approved by the local ethical committee in Stockholm and the subjects gave their written consent to participate in the study.

The subjects were screened for mental disorders including ADHD and BPD by a psychiatrist conducting a structured

interview using the M.I.N.I. (The Mini-International Neuropsychiatric Interview; Sheehan et al., 1998) and selected parts of the affective disorder evaluation (Sachs et al., 2003). Subjects completed a SCID-2 self-rating form (Structured Clinical Interview for DSM-IV Axis II Personality Disorders; First et al., 1997) (includes testing for BPD) and the ASRS (The World Health Organization Adult ADHD Self-Report Scale), which is a reliable self-rating test for ADHD (Kessler et al., 2005). Subjects also went through a neuropsychological testing procedure including IQ (Intelligence Quotient) testing using WAIS III (Wechsler Adult Intelligence Scale - Third Edition; Wechsler, 1997). Exclusion criteria included any ongoing mental illness (including ADHD), personality disorders (including borderline disorder), neurological conditions (except mild migraines), untreated endocrine disorders, dementia, recurrent depressive disorder and a first-degree relative with bipolar disorder or schizophrenia.

### Rating of subclinical symptoms associated with emotional dysregulation

We used Brown Attention Deficit Disorder Scale (B-ADDS) (Brown, 1996; Kooij et al., 2008) to rate subjectively experienced subclinical symptoms that are associated with emotional dysregulation. B-ADDS is widely used in the clinical setting, especially when testing for ADD/ADHD (Brown, 1996; Kooij et al., 2008), and focuses on problems in life. There are five clusters of questions: (i) organizing and activating for work, (ii) sustaining attention and concentration, (iii) sustaining energy and effort, (iv) managing affective interference and (v) utilizing 'working memory' and accessing recall. In order to simplify the phrasing for the two dimensions used in this study, we call the 'managing affective interference' cluster for the 'Emotion' block and the 'Sustaining attention and concentration' cluster for the 'Attention' block. While the Emotion block tests for symptoms associated with a dysfunctional top-down regulation of emotional processes, the Attention block tests for classical non-emotional attention problems often observed in ADHD. More specifically, the Emotion block includes questions focusing on difficulties managing emotions including frustration, anger, worry and disappointment. We chose the Emotion block for our main test and the Attention block for our control of non-emotional attention problems.

There are two reasons why this scale was used. First, it is one of the few self-rating scales incorporating both emotional and non-emotional attentional regulatory problems. Second, it measures symptom variability with a well-described distribution in the general population (Brown, 1996). This dimensional rather than categorical approach makes the instrument useful for capturing subclinical symptoms of emotional and non-emotional attentional regulation difficulties. The normative data for B-ADDS are presented in the reference manual (Brown, 1996).

### Acquisition and pre-processing of MRI data

For the B-ADDS analysis, MRI scans of 87 subjects, using a General Electric Signa Excite 1.5T and an 8-channel head coil, were acquired at the MR Research Centre, Karolinska University Hospital, Stockholm. About 1.8 mm slices of coronal images were acquired using a three-dimensional spoiled gradient echo recall sequence (3D-SPGR) with the following parameters: time to repetition = 21.0 ms, echo time = 6 ms, number of excitations = 1, flip angle = 30° and acquisition matrix = 256 × 256 × 124. To minimize motion artefacts, two

3D-SPGR series of images were acquired and then merged to a series of mean images in the pre-processing. This method produces images with less noise and has previously been used in other studies (Ekman et al., 2010). The pre-processing and analysis of images were performed with SPM8 statistical parametric mapping software (Wellcome Trust Centre for Neuroimaging; <http://www.fil.ion.ucl.ac.uk/spm>), and the voxel-based morphology (VBM) toolbox version 8 (Gaser, 2012). The method of VBM is characterized by a number of mathematical steps for pre-processing, which previously has been described in detail (Ashburner and Friston, 2000; Good et al., 2001). The two 3D-SPGR series of images were realigned and resliced to get a series of mean images for each subject, using highest quality, 1 mm separation between sampled points and applying a 2 mm full width at half maximum (FWHM) Gaussian smoothing kernel before estimating realignment parameters. The mean images were then manually reoriented to the anterior-posterior commissure line, all by the same investigator. Images were then segmented into grey matter, white matter and cerebrospinal fluid using the adaptive Maximum A Posterior technique (Rajapakse et al., 1997) applied in the VBM toolbox. Spatial normalization was performed using DARTEL normalization where the images were normalized to MNI space using a template derived from 550 healthy subjects (Ashburner, 2007). Grey matter images were modulated to compensate for spatial normalization and corrected only for non-linear warping. Because this study investigates relative volumes and only uses non-linear correction, there is no need to correct for differences in brain size in the statistical analysis (Gaser, 2012). All options for estimating and writing the SPMs in the VBM8 toolbox were set to default. The grey matter tissue maps were then smoothed using a 10 mm FWHM Gaussian kernel.

### Statistical analyses of MRI data

In the structural MRI analysis of GMV, the Emotion block rating and the Attention block rating for the included healthy subjects were entered as linear regressors and the voxel values of the smoothed images as the dependent variable in a mass univariate analysis. The Attention block regressor was used to control for processes that are associated with sub-clinical non-emotional attentional problems (see Introduction). Age and sex were used as covariates of no interest. A mask with an absolute threshold of 0.2 was applied to reduce the risk of including misclassified voxels in the analyses.

The search area was restricted using the WFU PickAtlas (Lancaster et al., 2000; Maldjian et al., 2003) to lObfc and ACC (including rACC) in our hypothesis-driven region of interest (ROI) search (see Supplementary Figure), and to insula, basal ganglia (including ventral striatum) and amygdala (emotional network ROI) in our exploratory ROI search in the remaining emotional network where we had no specific hypothesis about the direction of changes. Statistical significance was set to family-wise error (FWE)-corrected voxel level  $P < 0.05$ .

## Results

### Behavioural results

The degree of reported problems with emotional regulation and non-emotional attention regulation according to B-ADDS indicated that the subjects had no clinically relevant problems in these dimensions (Figure 1). Nevertheless, within this healthy group there was a significant variability in the Attention block

and the Emotion block ratings. Although the distribution was skewed for the Attention block and the Emotion block, the normalized difference between the Emotion block and the Attention block was normally distributed (Figure 1). The skewed distribution was due to floor effects, most likely because B-ADDS could not catch the more fine-grained variability.

### Reduced GMV related to emotional dysregulation

After controlling for age and gender, we showed that self-reported subclinical symptoms related to emotional dysregulation (Emotion block) were associated with robust decrease of GMV in lObfc when contrasted to non-emotional attention problems (Attention block) (Figure 2;  $[X, Y, Z] = -39\ 30\ -9$ , Z-value: 4.82, FWE-corrected P value: 0.001;  $[X, Y, Z] = 40\ 28\ -14$ , Z-value: 4.04, FWE-corrected P value: 0.020). We observed no significant volume decrease in rACC suggesting that structural changes in this region are associated with more pronounced emotional dysregulation (Soloff et al., 2008, 2012). These general results survived correction for several possible confounds including IQ (in a subset of subjects that had performed such testing) and whole brain analysis (see below).

We had no strong hypothesis about how other regions involved in emotional processing would be related to emotional dysregulation. Using an exploratory emotional network ROI, encompassing insula, basal ganglia (including ventral striatum) and amygdala in the original analysis, we observed that emotional regulation problems were associated with a significantly smaller insula on the left side ( $[X, Y, Z] = -40\ 24\ -8$ , Z-value: 4.56, FWE-corrected P value: 0.002;  $[X, Y, Z] = -34\ 11\ 0$ , Z-value: 3.96, FWE-corrected P value: 0.023), and a sub-significant threshold effect in right insula ( $[X, Y, Z] = 30\ 21\ 0$ , Z-value: 3.54, FWE-corrected P value: 0.091) and ventral striatum bilaterally ( $[X, Y, Z] = -6\ 8\ 1$ , Z-value: 3.44, FWE-corrected P value: 0.121;  $[X, Y, Z] = 8\ 8\ 0$ , Z-value: 3.33, FWE-corrected P value: 0.165) (Figure 3).

### Separate analysis of Emotion block and Attention block

Two different components contributed to the main finding presented above: (i) reported emotional regulation problems were associated with a decrease in lObfc volume and (ii) reported non-emotional attentional problems were associated with a reciprocal increase in lObfc volume (Figure 2B). Separate exploratory analysis shows that the Emotion block was negatively correlated with lObfc ( $[X, Y, Z] = -44\ 27\ -8$ , Z-value: 4.35, FWE-corrected P value: 0.006), while the Attention block was positively correlated with lObfc ( $[X, Y, Z] = 39\ 28\ -14$ , Z-value: 4.77, FWE-corrected P value: 0.001;  $[X, Y, Z] = -34\ 32\ -8$ , Z-value: 4.64, FWE-corrected P value: 0.002). Another way of illustrating this is to calculate the difference score between the Emotion block and the Attention block in the B-ADDS for each subject and use this difference score as a regressor in the VBM model (controlling for gender and age). This alternative analysis again showed large and bilateral volume decreases in lObfc ( $[X, Y, Z] = -38\ 30\ -9$ , Z-value: 4.92, FWE-corrected P value: 0.001;  $[X, Y, Z] = 40\ 28\ -14$ , Z-value: 4.51, FWE-corrected P value: 0.003).

In order to further explore the positive relationship found between GMV and Attention block with a more common rating scale for non-emotional attentional problems, we once again performed the analysis with ASRS. In this analysis, we show that the degree of rated non-emotional attentional problems indicated with the Inattention part in ASRS (i.e. the equivalent part to the Attention block in the B-ADDS) was positively correlated with the GMV in lObfc ( $[X, Y, Z] = -15\ 34\ -17$ , Z-value: 4.19,

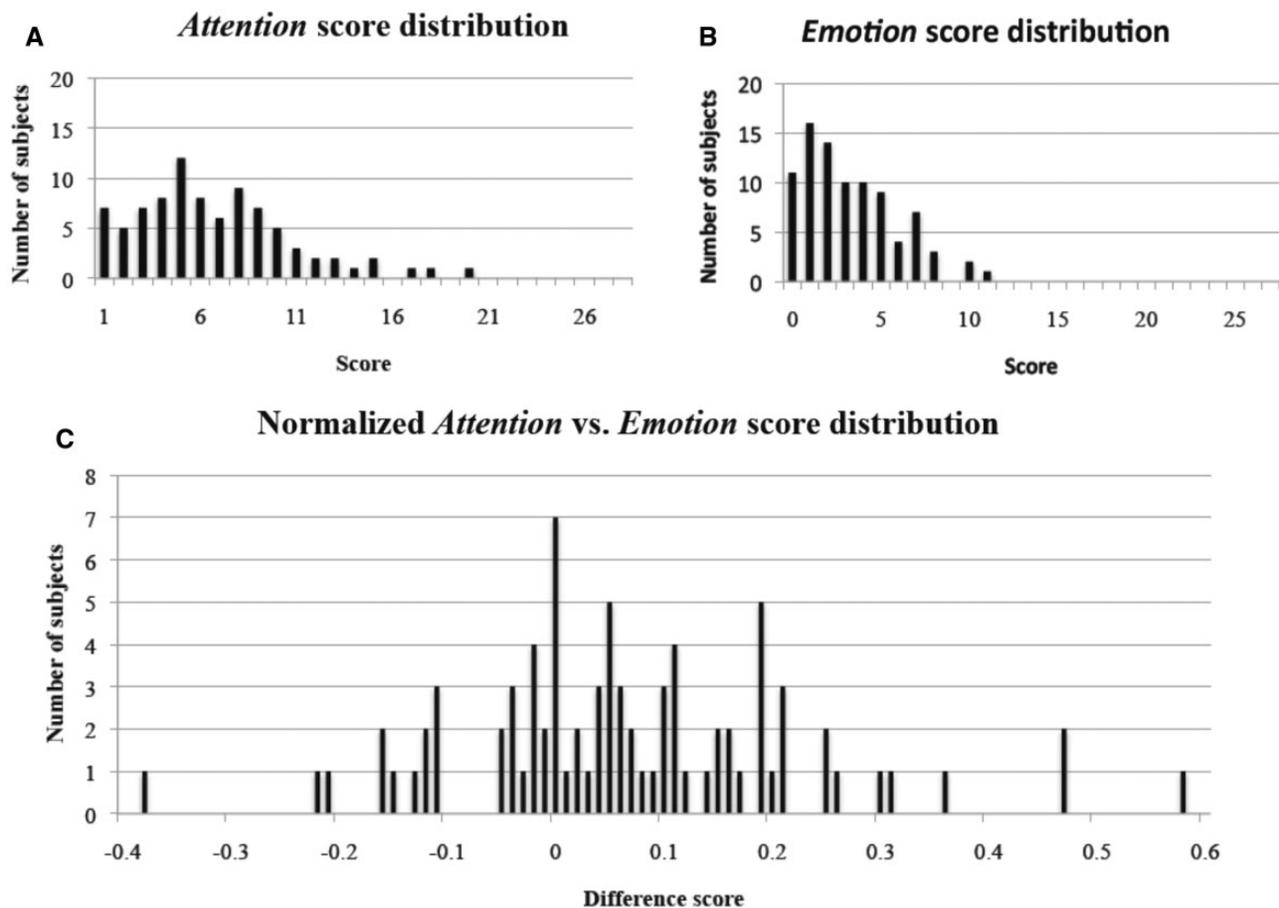


Fig. 1. Although the Attention score distribution (mean = 5.75, s.d. = 4.078) (A) and Emotion score distribution (mean = 3.30, s.d. = 2.642) (B) showed a skewed distribution among the subjects in Study 1 (significance for Kolmogorov-Smirnov score < 0.001 and < 0.01, respectively), the normalized Emotion vs Attention score (mean = 0.06, s.d. = 0.155) was normally distributed (significance for Kolmogorov-Smirnov score = 0.093) (C). The mean scores and standard deviations of the Attention block and the Emotion block for our sample are similar compared with the non-clinical sample that the normative data for B-ADDS (Brown, 1996) are based on ( $n = 143$ ; Attention score: mean = 7.5, s.d. = 4.6; Emotion score: mean = 5.4, s.d. = 3.2)—although the mean scores are somewhat lower in our sample. This difference may be caused by the stringent exclusion of subjects with psychiatric problems in this study. The clinical group with attention deficit disorder that the normative B-ADDS data are based on displayed significantly higher scores on these two dimensions (Attention score: mean = 18.6, s.d. = 4.7; Emotion score: mean = 12.3, s.d. = 3.9) (Brown, 1996).

FWE-corrected  $P$  value: 0.012)—thus confirming the finding above using another rating scale

### Correcting for IQ and handedness

In order to rule out that our results were caused by differences in IQ or handedness, we performed the main analysis where we controlled for these factors in 80 subjects for whom we had such data (i.e. 7 subjects had to be excluded in this analysis). IQ was tested using WAIS-III. Both handedness and the result from WAIS-III were added as extra regressors in the model that already corrected for gender and age. This analysis still showed that self-reported subclinical symptoms related to emotional dysregulation (Emotion block in B-ADDS) were significantly associated with a decrease of GMV in IObfc when contrasted with non-emotional attention problems (Attention block in B-ADDS) ( $[X, Y, Z] = -39\ 29\ -9$ ,  $Z$ -value: 4.52, FWE-corrected  $P$  value: 0.005;  $[X, Y, Z] = 41\ 27\ -14$ ,  $Z$ -value: 4.12, FWE-corrected  $P$  value: 0.051).

### Correcting for non-emotional questions in B-ADDS

A criticism of the main analysis may be that two of the questions in the Emotion block do not directly relate to emotional

problems but instead to autistic features (Questions 30 and 31). We therefore performed a version where we removed those questions from the analysis. The result of a relative decrease in IObfc volume remained for the contrast Emotion block vs Attention block ( $[X, Y, Z] = 42\ 27\ -15$ ,  $Z$ -value: 4.44, FWE-corrected  $P$  value: 0.004;  $[X, Y, Z] = -50\ 23\ -9$ ,  $Z$ -value: 4.11, FWE-corrected  $P$  value: 0.016).

Using the exploratory ROI (including ventral striatum, insula and amygdala) in the modified analysis (where non-emotional items in the B-ADDS Emotion block have been excluded) showed that emotional regulation problems were associated with a bilaterally smaller ventral striatum ( $[X, Y, Z] = 8\ 6\ 1$ ,  $Z$ -value: 3.89, FWE-corrected  $P$  value: 0.029;  $[X, Y, Z] = -10\ 6\ 0$ ,  $Z$ -value: 3.72, FWE-corrected  $P$  value: 0.051) and bilateral mid-anterior insula ( $[X, Y, Z] = 42\ 18\ -9$ ,  $Z$ -value: 3.75, FWE-corrected  $P$  value: 0.046;  $[X, Y, Z] = -32\ 8\ -2$ ,  $Z$ -value: 3.83, FWE-corrected  $P$  value: 0.036).

### Analysis of other possible regulatory regions

Although not part of our main hypothesis, we wanted to rule out that other prefrontal regions did not show an altered GMV. First, it has been shown that individual differences in habitual

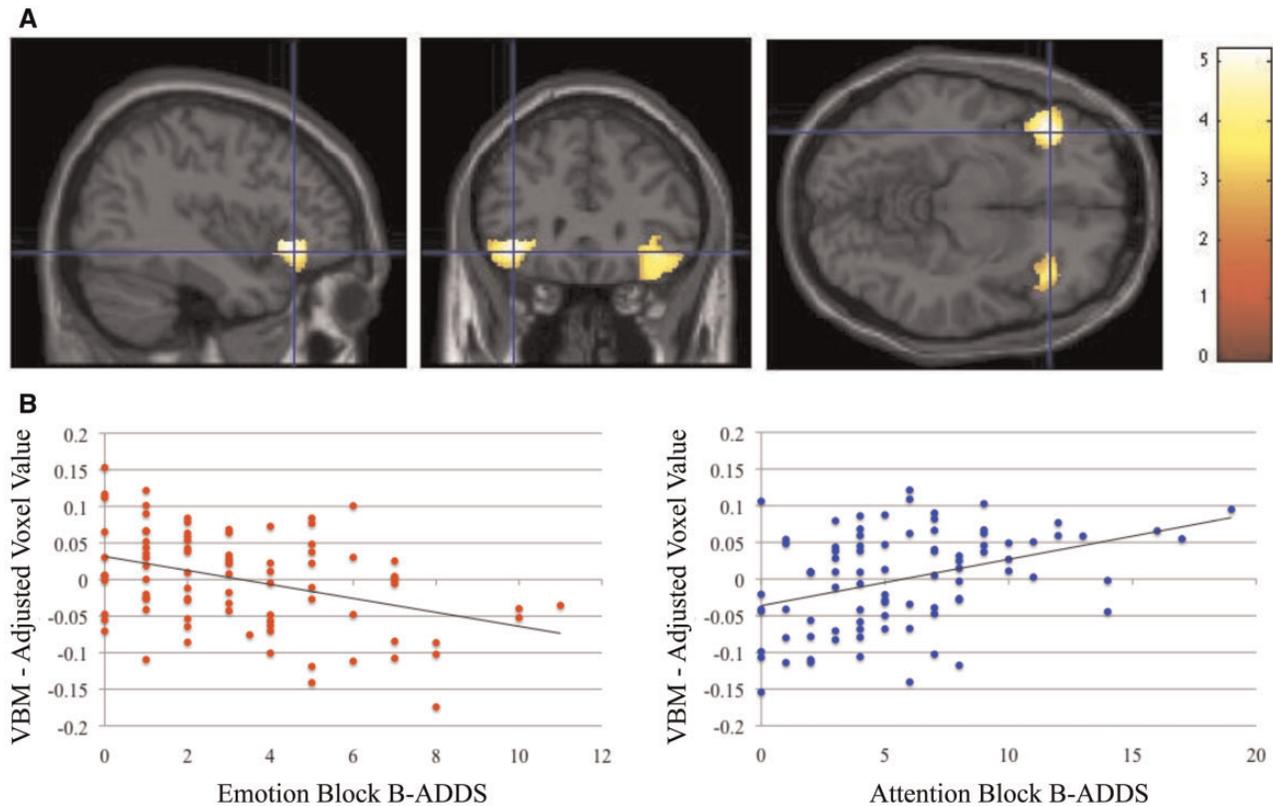


Fig. 2. (A) The VBM analysis showed that the lObfc volume was smaller in those subjects reporting larger problems with emotional regulation when contrasting the Emotion block with the Attention block in B-ADDS ( $[X, Y, Z] = -39\ 30\ -9$ , Z-value: 4.82, FWE-corrected P value: 0.001;  $[X, Y, Z] = 40\ 28\ -14$ , Z-value: 4.04, FWE-corrected P value: 0.020). The left lObfc activation also survived whole brain volume correction. The threshold for the SPM map was set to  $P < 0.005$  uncorrected. (B) This finding was attributed both to a decreased lObfc volume associated with symptoms of emotional dysregulation (red dots) and to an increased lObfc volume associated with attentional regulation problems (blue dots).

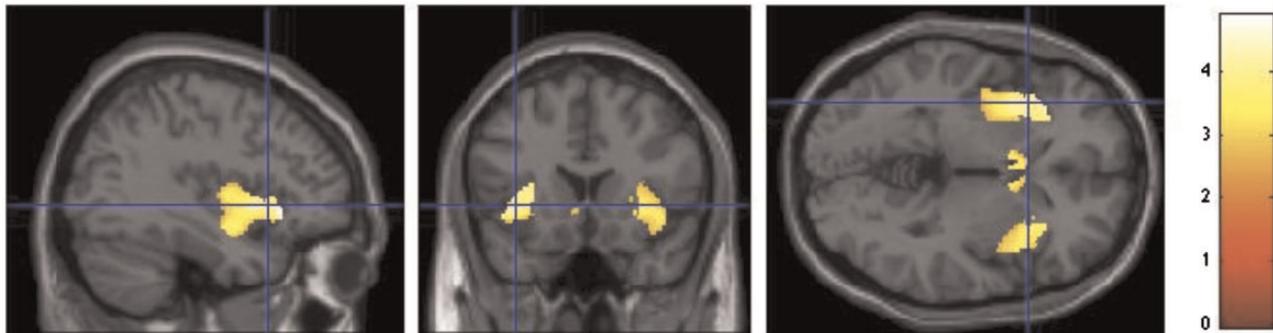


Fig. 3. An exploratory analysis of the VBM data in an emotional network including insula, ventral striatum and amygdala suggested that apart from lObfc other regions in the emotional network also decreased in volume including mid-anterior insula and ventral striatum (see Results). The cross-hair is focused on left insula ( $[X, Y, Z] = -34\ 11\ 0$ , Z-value: 3.96, FWE-corrected P value: 0.023). The threshold for the SPM map was set to  $P < 0.005$  uncorrected.

use of cognitive reappraisal strategies are associated with ventromedial PFC (vmPFC), but not lObfc, volume (Welborn et al., 2009). However, that questionnaire captures 'how much' a strategy is used overtly and not 'the capacity' of emotional regulation. To rule out an involvement of vmPFC, we specifically searched for a smaller GMV in vmPFC using an ROI approach that related to the Emotion block (Emotion block vs Attention block). No differences in GMV were observed (thresholded at  $P > 0.005$  uncorrected).

Second, according to our hypothesis, dlPFC is specifically involved in the non-emotional component during experimental emotional regulation tasks, e.g. the working-memory

component of holding a task instruction online. We therefore hypothesized that the volume should not be directly related to emotional regulation problems. To rule out a grey matter difference in this structure depending on emotional regulation problems, we performed an analysis within the rest of the PFC (using an ROI including dlPFC and vlPFC, i.e. ventrolateral prefrontal cortex). In this analysis, we observed no decreased volume in the Emotion block or in the contrast (Emotion block vs Attention block) in dlPFC (thresholded at  $P > 0.005$  uncorrected). However, we observed a significantly decreased volume in vlPFC in the main contrast (Emotion block vs Attention block) ( $[X, Y, Z] = -38\ 29\ -3$ , Z-value: 4.23, FWE-corrected P value:

0.018) and a sub-significantly decreased volume in vlPFC for the Emotion block ( $[X, Y, Z] = 42\ 33\ -3$ , Z-value: 3.89, FWE-corrected P value: 0.063) as well as an increased volume for the Attention block ( $[X, Y, Z] = -36\ 26\ -3$ , Z-value: 4.12, FWE-corrected P value: 0.028). Thus, these VBM findings mirrored the results in the main analysis for lObfc and represented a direct continuation of findings in lObfc.

Although not part of our initial hypothesis, we also performed an analysis to test whether there was any decreased GMV depending on problems with general attention in dlPFC. In this analysis, we observed no VBM decreases in the Attention block or for the contrast (Attention block vs Emotion block) in the prefrontal ROI including dlPFC and vlPFC (thresholded at  $P > 0.005$  uncorrected).

### Whole brain analysis

After correcting for whole brain volume, the only region that showed a significant decrease in GMV was left lObfc ( $[X, Y, Z] = -39\ 30\ -9$ , Z-value: 4.82, FWE-corrected P value: 0.0086) in the contrast (Emotion block vs Attention block) indicating the robustness in our main finding. No significant decrease was observed in the Emotion block specifically. In the whole brain analysis of the Attention block specifically, there was significant positive correlation between non-emotional attentional problems and GMV in left lObfc ( $[X, Y, Z] = -39\ 28\ -14$ , Z-value: 4.77, FWE-corrected P value: 0.011) and right lObfc ( $[X, Y, Z] = -34\ 32\ -8$ , Z-value: 4.64, FWE-corrected P value: 0.019). We also performed a whole brain analysis for the opposite contrasts without observing any significant VBM differences after correction for the whole brain volume.

### Discussion

In this study, we show that subclinical symptoms linked to emotional dysregulation are associated with a smaller GMV in the lObfc. This result suggests that the lObfc volume is associated with the capacity to regulate emotional processes. lObfc is involved in complex emotional regulation such as cognitive reappraisal of emotional stimuli (Eippert et al., 2007; Wager et al., 2008; Kanske et al., 2011; Golkar et al., 2012) and it has been suggested that it has critical role in psychiatric disorders displaying emotional dysregulation (Castellanos and Tannock, 2002; Lieb et al., 2004; Yang and Raine, 2009; Soloff et al., 2012) mirrored in lower functional activations in emotional regulation tasks (Wingenfeld et al., 2009; Yang and Raine, 2009; Schulze et al., 2011) and a smaller GMV (Yang and Raine, 2009; Soloff et al., 2012). Importantly, subjects in our studies were mentally healthy (see Materials and Methods and Figure 1). Thus, our results suggest that similar symptoms and underlying biological disturbances that are present in patients also are mirrored as a distribution in healthy individuals.

Even though the traditional concept of categorical psychiatric disorders has been challenged recently (Insel et al., 2010; Cuthbert and Insel, 2013), most previous research on mental disorders is based on this concept. The established theoretical framework has therefore lead to studies in search of discrete findings of psychopathology related to different diagnoses. This approach may hamper understanding of the involved mechanisms in the disorders and calls for a dimensional approach spanning the range from normal to abnormal (Insel et al., 2010; Cuthbert and Insel, 2013). Research of processes and symptoms directly related to psychiatric disorders in healthy subjects has therefore been initiated (Ersche et al., 2012; Robbins et al., 2012),

although there are few accounts in the literature of a direct variability of clinical symptoms in healthy subjects.

Studying functional or structural variability in healthy individuals, as in this study, complements the research on neurocognitive endophenotypes oriented towards next of kin to patients carrying psychiatric diagnoses (Ersche et al., 2012; Robbins et al., 2012). The main difference is that our approach has a less expressed categorical stance (as 'next of kin studies' may also be interpreted as defining categories consisting of patients and their relatives in relation to healthy controls). Thus, a true continuum in biological processes relating to subclinical psychiatric symptoms in healthy populations more strongly supports a dimensional view of psychiatry. This approach has successfully been implemented in some functional imaging studies (Bishop, 2009; Indovina et al., 2011; Whelan et al., 2012) but rarely been used in structural brain imaging—possibly because of the requirement of a large number of participants for such an analysis.

In this study, we measured a range of subclinical symptoms that are related to emotional and non-emotional attention dysregulation. This contrasts to studies focusing on a specific process, such as motor inhibition in the Stop-signal task (Whelan et al., 2012). It is well-known that patients regularly display several symptoms while specific tests only focus on one sub-process and cannot identify a large proportion of the patients (Castellanos and Tannock, 2002). Using a specific test such as the Stop-signal task may therefore decrease sensitivity (although it may also give more precise information about the involved sub-components). This would be especially important if there is a more general deficient mechanism that may affect distinct sub-processes in different subjects. Here, we hypothesized that top-down (emotional and non-emotional) dysregulation is causing a range of symptoms including impulsivity (the key component measured in the Stop-signal test) as well as other symptoms linked to the more general deficient top-down regulatory mechanism.

Although reported emotional regulation problems were associated with a decrease in lObfc volume, reported non-emotional attentional problems were associated with a reciprocal increase in lObfc volume (Figure 2B). These findings are in line with a well-powered study of ADHD that had controlled for affective dysfunctions (Seidman et al., 2011). In that study an increased volume of lObfc bilaterally and rACC was observed in ADHD patients compared with controls, in conjunction with the expected decreased volume in non-emotional attentional systems including dlPFC and cACC that has previously been well-described for ADHD patients. Moreover, emotional regulatory systems decrease in activity when non-emotional attentional systems are active (Simpson et al., 2000) and vice versa (Dolcos and McCarthy, 2006), and resting state studies have suggested that rACC and cACC belong to anti-correlated networks (Fox et al., 2005; Fransson, 2005; Castellanos and Proal, 2012). These findings suggest that emotional and non-emotional regulatory systems may be mutually inhibitory. An intriguing possibility is therefore that if one of these two regulatory systems is deficient the other regulatory system becomes relatively more active, and that such an imbalance would promote structural brain changes over time. A difference in the balance between these two regulatory systems could also explain why misuse of substances (indicative of emotional impulsivity) is related to hypofunctioning of lObfc, while non-emotional ADHD traits are related to hypofunctioning in dlPFC during stop-signal task (Whelan et al., 2012). We suggest that lObfc involvement is only found in the most aggravating variants of BPD (Soloff et al., 2008,

2012) because ADHD and BPD are highly associated (Philipsen et al., 2008) and non-emotional attentional regulation problems are seldom controlled for. Thus, our data strongly imply that not correcting for non-emotional attentional regulation problems in patients displaying emotional dysregulation may obscure relative dysfunction in emotional regulation networks.

Both earlier tracing studies on primates including humans (Ongur and Price, 2000) and more modern functional imaging-based connectivity studies in humans (Kahnt et al., 2012; Zald et al., 2014) have indicated a different connectivity dependent on a mediolateral and anterior–posterior division of the Obfc—although a more complex picture emerges at a finer scale. It has been suggested that this distinction has certain functional consequences (Kringelbach and Rolls, 2004). In this study, our findings are restricted to a lateral–posterior part of the lObfc. Given previous connectivity studies (Ongur and Price, 2000; Kringelbach and Rolls, 2004; Kahnt et al., 2012; Zald et al., 2014), this part of the lObfc has the potential to interact both with regions thought to be involved in emotional processes such as insula, amygdala and ventral striatum as well as inferior rostral/lateral PFC—although our findings cannot perform detailed discriminations between different subdivisions of Obfc because of smoothing and voxel size.

An exploratory search in the emotional network outside the hypothesis-driven ROIs showed that self-reported problems with emotional regulation were associated with a smaller insula and ventral striatum (Figure 3) in line with two large VBM studies on BPD that showed pronounced decreased volume in insula bilaterally (Soloff et al., 2008, 2012). All together, these results suggest that also parts of downstream emotion processing system are involved in aspects of emotional control, probably in interaction with top-down regulatory regions.

Our data indicate that emotional regulation capacity indexed by subclinical symptoms in the emotional domain is associated to lObfc volume in healthy individuals. However, it has to be underlined that the association between smaller GMV and underlying function is not straightforward. Brain volume is dependent not only on neurons and synapses but also on non-neuronal cells (such as glia cells) and other tissue. Even at neuronal level some networks may be associated with increased activity, while others may be inhibitory complicating the interpretation of volume differences. There seems to be a link between structure and function in clinical states such as ADHD and BPD. For example, in ADHD, smaller GMV in dlPFC and cACC has been observed (Seidman et al., 2011), and these structures are less activated during attentional tasks in this group (Dickstein et al., 2006). Likewise, in BPD, smaller GMV has been observed in lObfc and rACC (Soloff et al., 2008, 2012) and these regions are less activated in emotional regulation for this group of patients (Wingenfeld et al., 2009; Schulze et al., 2011). At the same time, BPD is linked to smaller volume in insula and amygdala (Soloff et al., 2008, 2012) but an over-activity of these regions in emotional processes (Herpertz et al., 2001; Donegan et al., 2003; Hazlett et al., 2012)—possibly suggesting a reduced volume in local inhibitory networks. Further studies are therefore needed in order to better understand what the functional significance of smaller lObfc related to sub-clinical emotional dysregulation actually represents.

It is undoubtedly clear that emotional and non-emotional processes interact on every level at the different hierarchies in the brain (Pessoa, 2008). Few regions are involved in just ‘emotional’ or ‘non-emotional’ processes, and it may be hard to disentangle non-emotional attentional regulation from emotional control networks. It is, e.g. important to note that the Obfc also

is involved in breaches of attention (Nobre et al., 1999) and implicated in the expectation-mediated facilitation of perceptual decision making and object recognition (Bar et al., 2006). However, at the same time, our data suggest that there is something unique with how clinical failure of emotional vs non-emotional top-down regulation is mirrored in the underlying structure of PFC.

In summary, our finding in healthy subjects translates to a dysfunctional top-down control system in lObfc and related areas suggested for emotional ADHD, ADS and BPD (Castellanos and Tannock, 2002; Lieb et al., 2004; Wingenfeld et al., 2009; Yang and Raine, 2009; Schulze et al., 2011, 2012) including a smaller GMV in patients displaying emotional dysregulation (Yang and Raine, 2009; Soloff et al., 2012). Reduced lObfc volume has also been observed in adult subjects previously classified as high-reactive infants (Schwartz et al., 2010) and for cumulative adverse life events in chronically stressed subjects (Ansell et al., 2012)—groups that often display emotional dysregulation. In healthy volunteers it has been observed that there is a relationship between the tendency to conform to values expressed by others and lObfc volume (Campbell-Meiklejohn et al., 2012) suggesting a lower capacity to regulate emotional conflicts that arise between internal and external judgments. Taken together with present findings, these studies support a dimensional view on psychiatric disorders associated with emotional dysregulation spanning from healthy individuals to patients rather than a categorical divide.

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## Supplementary data

Supplementary data are available at SCAN online.

Conflict of interest. None declared.

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