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Brief report

Altered patterns of brain activity during transient sadness in children at familial risk for major depression

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ABSTRACT

Introduction: We used functional magnetic resonance imaging (fMRI) to investigate the neural correlates of sadness, the prevailing mood in major depression (MD), in a prospective, well-documented community sample followed since birth.
Methods: The children, comprising 136 children (65 boys and 71 girls) of mothers with varying levels of depressive symptomatology, were scanned – using a 1.5-Tesla system – while they watched 5 blocks of both sad and neutral film excerpts. Following scanning, they rated the emotions they experienced, and if they identified sadness, they were also asked to rate its intensity.
Results: In children whose mothers exhibited higher depressive symptomatology, compared to children whose mothers displayed lower depressive symptomatology, altered neural responses to sad film excerpts were noted in brain regions known to be involved in sadness and MD, notably the insula, anterior cingulate cortex and caudate nucleus, even though the children did not differ in current mood.
Limitations: Whether this represents genetic vulnerability or a consequence of exposure to maternal depressive symptoms at a young age is unknown.
Discussion: The results are consistent with the results of studies in healthy adults and MD patients. The present study suggests that an altered pattern of regional brain responses to sad stimuli, is already present in childhood and might represent vulnerability for MD later in life.

1. Introduction

Findings from a number of neuroimaging studies indicate that the activity of brain regions involved in emotional processing, such as the amygdala, insula and lateral orbitofrontal cortex (LOFC), is altered in individuals with major depression (MD) during a transient state of sadness (Beauregard et al.,

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2004; Beauregard et al., 2006; Levesque et al., 2003). Such functional alterations may be related, at least in part, to a dysfunction of the neural circuitry underlying emotion regulation. In accordance with this view, there is considerable evidence that an inability to regulate emotions effectively plays a pivotal role in MD (Kring and Bachorowski, 1999). Emotion regulation is mediated by various prefrontal cortical areas, including the medial orbitofrontal cortex (MOFC) and the anterior cingulate cortex (ACC) (Beauregard et al., 2004). The functioning of these prefrontal areas is known to be altered in individuals with MD (Beauregard et al., 2006; Phillips et al., 2008).

Early childhood adversities may influence the risk for MD later in life. Regarding this issue, it has been shown that offspring of parents with MD have a threefold greater risk for this disorder than offspring without such family histories (Weissman et al., 2006). A familial risk for MD may exert a negative impact on brain development, with deleterious consequences for the cerebral structures implicated in emotional processing and emotion regulation (Beauregard et al., 2004; Forbes et al., 2006; Maughan et al., 2007). Nothing is known yet with respect to this important question. Given that MD often develops in adolescence (Kessler et al., 2001), it is of further relevance to explore this issue in younger children, to investigate whether brain activation can predict later depressive symptoms.

This study investigated neural correlates of sadness, the prevailing mood in MD, in a prospective, community sample comprising children of mothers with varying levels of depressive symptoms who have been regularly followed since birth. Neural activation was measured during a mood induction task which consists of neutral and sad film extracts utilized in previous studies (Cote et al., 2007; Eugene et al., 2003; Levesque et al., 2003) to induce temporary sadness. We hypothesized that greater levels of depressive symptoms in the mother would be associated with altered functioning of regions associated with emotion during a mood induction task during childhood, notably the OFC, ACC, insula, amygdala, hippocampus and caudate nucleus.

2. Methods

2.1. Participants

Participants were 136 children (65 boys and 71 girls) from the Quebec Study of Newborn Twins (QSNT; (Brendgen et al., 2005; Forget-Dubois and Perusse, 1997), who were scanned using functional magnetic resonance imaging (fMRI) when they were 8 years and 4 months of age (Cote et al., 2007). The research protocol was approved by the appropriate ethics committees. Written consent was obtained from parents of all participants and oral assent from participants. In some cases, scans from both twins were used; in others one was excluded due to head movement (64 single twins; 36 twin pairs or 72 individuals).

2.2. Measures

The Dominic-R interview based on the DSM-IV was used to evaluate the mental health of the participants (Valla et al., 2000). The different groups scored below clinical cut-off scores for all mental health problems assessed with this measure, including MD, anxiety, ADHD and conduct problems. In regards to depressive symptomatology, the children's scores were within a healthy range and not statistically different between the two groups (HD: mean = 6, s.d. = 4.30; LD: mean = 5.30, s.d. = 3.50). Maternal depressive symptoms were assessed using the Symptom Checklist (SCL-90) (Derogatis, 1983; Derogatis, 2000) when the children were 5, 18, 30 and 48 months, and averaged over these time points. Children whose mothers exhibited higher depressive symptomatology (Group HD, highest third of sample, n = 45; mean = 61.6, s.d. = 4.2) were compared to children whose mothers displayed lower depressive symptomatology (Group LD, lower two thirds, n = 91; mean = 48.6, s.d. = 5.1). The decision to compare the highest third of the sample in depressive symptoms to the lower two thirds was made given that we used a healthy, non-clinical sample, in order to approximate depressive symptomatology in the high group. Members of the HD group also had significantly lower family income (defined as 30000 $ or less) than members of the LD group, which could indicate an interaction or an additive effect of these two adversity factors.

Following Fortier et al. (2010), T2* weighted functional images were acquired on a 1.5-Tesla system (Magnetom Vision, Siemens Electric, Erlangen, Germany), using an echoplanar image (EPI) pulse sequence (time repetition (TR) = 0.8 ms, time-echo (TE) = 54 ms, flip = 90°, field of view (FOV) = 215 mm, matrix = 64 × 64, voxel size = 3.36 mm × 3.36 mm × 5 mm). Twenty-eight 5 mm slices were acquired every 2.65 s in an inclined axial plane, aligned with the anterior commissure–posterior commissure axis. High-resolution data were then acquired via T1-weighted 3-D volume acquisition using a gradient echo pulse sequence (TR = 9.7 mm, TE = 4 ms, flip = 12°, ROV = 250 mm, matrix = 256 × 256, voxel size = 0.94 mm^3).

2.3. Procedure

Participants underwent a functional scan while they watched five 39-second blocks of emotionally neutral film excerpts (TV news interview) followed by five 39-second blocks of sad film excerpts (clip depicting death of a father) (Gross and Levenson, 1995). This order was used in order to avoid contamination of neutral stimuli by emotional stimuli. Blocks were separated by 15-second resting periods consisting of fixation of a cross. After scanning, participants identified the primary emotions they felt during the sad and neutral excerpts using a visual analog scale. If participants identified sadness, they were asked to rate its degree (1: sad, 2: very sad, 3: extremely sad, 4: saddest ever) (Cote et al., 2007).

2.4. Analyses

Pre-processing steps were done using SPM5 (Wellcome Department of Cognitive Neurology, London UK) in accordance with Fortier (Fortier et al., 2010). Images of all participants were realigned to correct for small head movements and spatially normalized into an EPI stereotactic space (Montreal Neurological Institute template). This template was then used to derive Talairach and Tournoux (1988) coordinates defining the ROIs. Next, images were convolved with a 3-D isotropic Gaussian kernel at 12 mm full width half maximum in order to improve