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Decoupling of the amygdala to other salience network regions in adolescent-onset recurrent major depressive disorder

R. H. Jacobs[1], **A. Barba**[1], **J. R. Gowins**[1], **H. Klumpp**[1], **L. M. Jenkins**[1], **B. J. Mickey**[2], **O. Ajilore**[1], **M. Peciña**[2], **M. Sikora**[2], **K. A. Ryan**[2], **D. T. Hsu**[2,3], **R. C. Welsh**[2,4], **J.-K. Zubieta**[2,4], **K. L. Phan**[1,5], and **S. A. Langenecker**[1,*]

[1]Department of Psychiatry, University of Illinois at Chicago, Chicago, IL, USA

[2]Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA

[3]Department of Psychiatry, Stony Brook University, Stony Brook, NY, USA

[4]Department of Radiology, Molecular and Behavioral Neuroscience Institute, Ann Arbor, MI, USA

[5]Mental Health Service Line, Jesse Brown VA Medical Center, Chicago, IL, USA

Abstract

Background—Recent meta-analyses of resting-state networks in major depressive disorder (MDD) implicate network disruptions underlying cognitive and affective features of illness. Heterogeneity of findings to date may stem from the relative lack of data parsing clinical features of MDD such as phase of illness and the burden of multiple episodes.

Method—Resting-state functional magnetic resonance imaging data were collected from 17 active MDD and 34 remitted MDD patients, and 26 healthy controls (HCs) across two sites. Participants were medication-free and further subdivided into those with single *v.* multiple episodes to examine disease burden. Seed-based connectivity using the posterior cingulate cortex (PCC) seed to probe the default mode network as well as the amygdala and subgenual anterior cingulate cortex (sgACC) seeds to probe the salience network (SN) were conducted.

Results—Young adults with remitted MDD demonstrated hyperconnectivity of the left PCC to the left inferior frontal gyrus and of the left sgACC to the right ventromedial prefrontal cortex (PFC) and left hippocampus compared with HCs. Episode-independent effects were observed between the left PCC and the right dorsolateral PFC, as well as between the left amygdala and right insula and caudate, whereas the burden of multiple episodes was associated with hypoconnectivity of the left PCC to multiple cognitive control regions as well as hypoconnectivity of the amygdala to large portions of the SN.

[*]Address for correspondence: S. A. Langenecker, Ph.D., Department of Psychiatry, University of Illinois at Chicago, 1601 W. Taylor Street, M/C 912, Chicago, IL 60612, USA. slangenecker@psych.uic.edu.

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Supplementary material

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Declaration of Interest

None.

Conclusions—This is the first study of a homogeneous sample of unmedicated young adults with a history of adolescent-onset MDD illustrating brain-based episodic features of illness.

Keywords

Amygdala; connectivity; depression; functional magnetic resonance imaging; illness course

Introduction

Emerging research has documented network abnormalities present during the resting state related to major depressive disorder (MDD). However, understanding the relevance and degree to which these network abnormalities relate to clinical features of illness and course of illness has only begun (Kerestes *et al.* 2012; Dichter *et al.* 2015). In particular, it is unclear whether relative hypo- and hyperconnectivity patterns within and between key networks are stable and trait-like or whether they stem directly from the acute disturbance of illness. Episodic, compensatory and burden features are likely to contribute to within-and between-study variability, obscuring key breakthroughs in understanding mechanisms of illness and prohibiting development of targeted treatments for MDD (Weisenbach *et al.* 2014). As studies of currently active illness dominate the literature, meta-analytic studies are likely to miss nuances discriminating episodic features of MDD (Pizzagalli, 2011).

One approach to begin to examine the distinctions inherent in a multiply determined, multiply defined illness such as MDD is to examine individuals as they pass through phases of illness including the acute disturbance of a depressive episode as well as remission and relapse. Examining these phasic patterns is also clinically relevant given an adequate understanding of risk for relapse in the remitted phase of MDD could help reduce public health burden via secondary prevention. The risk of repeated episodes increases as a function of previous episodes (Keller *et al.* 2007) and 70% of individuals in remission are at risk for future episodes. Adequate maintenance and novel interventions focused on secondary prevention have not been adequately explored to date.

Abnormalities in resting-state network connectivity have been consistently reported in MDD (Sundermann *et al.* 2014; Kaiser *et al.* 2015) and hyper-connectivity within the default mode network (DMN) may be the most commonly identified network abnormality in MDD (e.g. Sheline *et al.* 2009; Hamilton *et al.* 2015). The DMN was originally observed in the context of task-based studies to describe ‘task-negative’ regions that decrease in activation during performance of attention-demanding tasks and increase in activation during rest, mind-wandering or self-reflective thought (for a review, see Whitfield-Gabrieli & Ford, 2012). In contrast, a task-positive network includes regions that increase in activation during attention to demanding tasks (Fox *et al.* 2005). Task-positive and task-negative networks appear to act in opposition. For example, they have been shown to be anticorrelated during both cognitive tasks and during the resting state.

Two important, dissociable task-positive networks are the executive network (EN) and salience network (SN; Seeley *et al.* 2007). The SN supports emotion processing and autonomic regulation and incorporates regions such as the dorsal anterior cingulate cortex (ACC) and the orbital frontoinsula (Seeley *et al.* 2007). The SN overlaps with the affective

network in regions such as the insula and regions of the SN are functionally connected with the cognitive control network (CCN) and DMN; thus, the SN is not strictly task-positive (Menon & Uddin, 2010). Dysfunction in the SN contributes to biases in emotion processing and autonomic regulation (Drevets *et al.* 2008; Briceño *et al.* 2013; for a review, see Price & Drevets, 2010). In contrast, the EN (also described as the CCN), modulates responses to stimuli that have already been identified as salient (Seeley *et al.* 2007; Menon, 2011). Taken together, aberrant network functioning may underlie and perpetuate observable clinical symptoms such as rumination (DMN), emotional dysregulation (CCN) and emotional reactivity (SN, e.g. Hamilton *et al.* 2012) exemplifying network models of psychopathology (Bressler & Menon, 2010; Menon, 2011).

Evidence that resting-state networks are disrupted in MDD has reinvigorated attempts to better parse clinical characteristics of illness as well as to understand putative markers of early treatment response and illness course. For example, a recent review of resting-state functional magnetic resonance imaging (fMRI) within the context of treatment response highlighted hyperconnectivity within the DMN and hypoconnectivity within the CCN in distinguishing individuals with treatment-resistant depression (de Kwaasteniet *et al.* 2015; Dichter *et al.* 2015). Treatment response, in contrast, appears to be associated with increased connectivity between frontal and limbic brain regions, possibly refiecting increased control over emotion processing and regulation (also see Crowther *et al.* 2015). An investigation of neural network markers of illness course and burden is both necessary and timely in advancing research on early identification, prospective clinical course prediction and novel treatment targets; however, limited work to date has exploited the opportunity to examine differences across phases of illness in unipolar depression. In bipolar illness, some evidence has begun to emerge as network connectivity captured during task-based fMRI has been used to demarcate manic from depressive episodes among individuals with bipolar disorder (e.g. Perlman *et al.* 2012). In sum, foundational knowledge of network disruptions may assist in the identification of novel treatment targets.

We previously compared young adults in the remitted phase of MDD (rMDD) with healthy controls (HCs) and found hyperconnectivity of the DMN, as indexed by the posterior cingulate cortex (PCC) seed, and SN, as indexed by the subgenual ACC (sgACC) and amygdala seeds, with the CCN and that these differences were related to rumination and sustained attention (Jacobs *et al.* 2014). Thus, we sought to extend this novel work by comparing rMDD with active MDD (aMDD) to examine whether the observed network abnormalities were similar or distinct during different states of illness course (in *v.* out of episode). We also undertook a second analysis to investigate the influence of multiple episodes (i.e. illness burden). In order to extend upon our previous work we used the same PCC, sgACC and amygdala seeds as probes of the DMN and SN.

In sum, unanswered questions of clinical importance remain regarding the direction and extent of disrupted neural connectivity in MDD, particularly in relation to vulnerabilities that remain into remission and may point to pre-illness risk factors. We hypothesized that we would replicate our finding of increased connectivity within and between regions of the DMN (as indexed by seed-based connectivity of the PCC with the whole brain) and within and between the SN (as indexed by connectivity of the sgACC and amygdala seeds to the

whole brain) among unmedicated young adults with rMDD compared with HCs. We hypothesized that these identified patterns in rMDD would differ from peers in the active state of illness and that hypoconnectivity would be observed among aMDD patients compared with both HCs and rMDD patients. Furthermore, we hypothesized that overall patterns of network connectivity would distinguish all MDD (both rMDD and aMDD) from HCs (episode-independent effect) as well as distinguish aMDD from rMDD (episode-dependent effect; Mayberg *et al.* 1999; Harrison *et al.* 2008). Last, as a secondary investigation into the nuances inherent to MDD, we investigated whether illness burden – defined as number of episodes – was associated with differential connectivity patterns.

Method

Participants

The current study was approved by the University of Michigan (UM) and the University of Illinois at Chicago (UIC) Institutional Review Boards. After a complete description of the study to participants, written informed consent was obtained. All participants completed structured diagnostic interviews (see online Supplementary material). Participants were considered rMDD if they previously met criteria for at least one major depressive episode (MDE) and scored below seven on the Hamilton Rating Scale for Depression (HAM-D; Hamilton, 1960). aMDD individuals were experiencing a current MDE and scored higher than 12 on the HAM-D. HCs did not meet current or past criteria for MDD or any other Axis I or II psychiatric disorder and had no first-degree relatives with a history of psychiatric illness. In addition, participants were required to be medication free for a minimum of 14 days prior to the scan (0 individuals were on fluoxetine, which has a longer half-life, and the majority had not received medication for over 3 months), and those with substance abuse or dependence within the past 6 months were excluded. An initial sample of 103 individuals in the 18–25 years age range was preprocessed and outliers were removed based on movement (see online Supplementary material). A final sample of 77 individuals with usable fMRI data included 17 aMDD, 34 rMDD and 26 HCs (n = 50 female, 65% female; demographic differences between the usable and full sample are reported in the online Supplementary material). These individuals were further subdivided based on level of burden, with 15 individuals reporting a single episode (three aMDD, 12 rMDD) and 29 individuals reporting multiple episodes (11 aMDD, 18 rMDD). Data on number of episodes were not available for seven individuals in the final sample.

fMRI acquisition

Both sites included an eyes-open resting-state scan acquired over 8 min. At UM (17 HC, 17 rMDD, 10 aMDD), scans were collected with a 3.0 T GE Signa scanner (USA) using T2*-weighted single shot reverse spiral sequence with the following parameters: 90 degree flip, field-of-view 20, matrix size = 64 × 64, slice thickness = 4 mm, 30 ms echo time, 29 slices. Scans at UIC (nine HC, 17 rMDD, seven aMDD) were collected with a 3.0 T GE Discovery scanner (USA) using parallel imaging with ASSET and T2* gradient-echo axial echo planar imaging (EPI) with the following parameters: 90 degree flip, field-of-view 22, matrix size = 64 × 64, slice thickness = 3 mm, 22.2 ms echo time, 44 slices, with a repetition time (TR) of 2000 ms with a total of 240 TRs collected. At both sites, high-resolution anatomic T1 scans

were obtained for spatial normalization and motion was minimized with foam pads, a visual tracking line (UIC only) and/or cross (UIC and UM) on the display, and by conveying the importance of holding still to participants, with a TR of 2000 ms and 240 TRs collected.

fMRI preprocessing

Slice timing, realignment, co-registration, warping [DARTEL to Montreal Neurological Institute (MNI) template] and smoothing (5 mm full width at half maximum) were all completed with SPM8 batch scripts, including visual inspection after each step (see online Supplementary material).

Cross-correlation analysis

Time series was detrended and mean centered. Physiological correction was performed by regressing out mean signal from white matter and cerebral spinal fluid (Behzadi *et al.* 2007). Motion parameters and deviations in pitch, roll and yaw were regressed out within first-level models (Jo *et al.* 2013). Global signal was not regressed due to collinearity violations with gray matter signal, problematic misestimates of and introductions of anticorrelations (Fox *et al.* 2009), and effect on distance–micromovement relationships (Jo *et al.* 2013). Finally time-series were band-pass filtered over 0.01–0.10 Hz. Seeds were derived based on previous literature examining resting-state connectivity of the PCC to examine the DMN (Bluhm *et al.* 2011; Alexopoulos *et al.* 2012) as well as the amygdala (McCabe & Mishor, 2011; Pannekoek *et al.* 2013) and sgACC (Margulies *et al.* 2007; Kelly *et al.* 2009) to probe the SN. The following coordinates were used: PCC (DMN, −5, −50, 36), amygdala (SN, −23, −5, −19), sgACC (SN, −4, 21, −8), with left coordinate seeds. Two SN seeds were used in light of prior work (Jacobs *et al.* 2014) suggesting that these two seeds do not capture entirely overlapping networks among healthy individuals when using seed-based strategies.

Correlation coefficients were calculated between mean time course for seed regions and all other voxels of the brain, resulting in three-dimensional correlation coefficient images (r images), transformed to *Z* scores using a Fisher transformation and compared in SPM8. Whole-brain correction was achieved at $p < 0.05$ by conducting 1000 Monte Carlo simulations in AlphaSim to determine a joint threshold of height and extent ($p < 0.005$, cluster extent of 440 mm^3).

Statistical analyses

Two random-effects multivariate analyses of covariance (MANCOVAs) were computed. The first examined disease and episodic (episode-independent effects) effects by comparing aMDD, rMDD and HCs, covarying for sex and site. The second random-effects MANCOVA addressed disease burden by comparing HCs, individuals with a single MDE and those with multiple MDEs, from both the active and remitted groups, covarying for HAM-D score, sex and site. We report and display findings meeting group-level *F* test thresholds and interpret regions of main group effects through examination of *post-hoc* tests. None of these results was influenced by site as reported in the online Supplementary material. We also tested whether any identified group differences were related to age of participant or to clinical features including level of depression and anxiety using the HAM-D and Hamilton Rating Scale for Anxiety.

Results

Participant demographics and clinical characteristics

Table 1 details the current sample. Individuals in the aMDD group reported higher HAM-D scores [$F = 291.11$, degrees of freedom (df) = 2, $p < 0.01$] and a greater number of MDEs ($F = 16.36$, df = 2, $p < 0.01$) than individuals in the rMDD group and HCs. In addition, more individuals in the aMDD group had a history of co-morbid anxiety disorders ($F = 25.55$, df = 2, $p < 0.01$), endorsed using psychiatric medications in the past ($\chi^2 = 7.25$, df = 1, $p = 0.03$) and were approximately 1 year older ($F = 4.18$, df = 2, $p = 0.02$) than aMDD and HCs. Individuals with multiple MDEs (hereafter ME MDD, mean = 13.82, S.D. = 3.48) compared with a single MDE (hereafter SE MDD, mean = 18.20, S.D. = 2.70; $F = 17.92$, df = 1, $p < 0.01$) reported an earlier age of illness onset but did not differ from the single episode group on any other clinical or demographic feature including family history (all $p > 0.05$).

All figures display results meeting *F* test thresholds only, with *post-hoc* contrasts indicated in Tables for only those regions surviving whole-brain correction with *F* test significance.

Episode-dependent and -independent connectivity of the PCC

Fig. 1 illustrates PCC seed-based connectivity differences for the main effect of group (*F* tests, blue). *F* test group differences were observed in three regions: the left inferior frontal gyrus (IFG), right middle frontal gyrus (MFG) and adjacent areas to the seed within the left PCC. In contrast, participants with aMDD demonstrated weakened connectivity to the left IFG compared with rMDD, suggestive of an episode-dependent feature of illness. In addition, participants with aMDD demonstrated amplified connectivity within the DMN (i.e. to adjacent portions of the PCC) compared with rMDD, also suggestive of an episode-dependent feature of illness. Table 2 details significant group differences and the direction of *post-hoc* effects indicating clinical correlations. In contrast, all MDD demonstrated amplified connectivity of the left PCC to the right MFG compared with HCs, suggestive of an episode-independent feature of illness.

Episode-dependent connectivity of the amygdala

All MDD demonstrated amplified connectivity of the left amygdala with the right anterior insula, caudate and claustrum compared with HCs, indicative of state-independent features of illness (Fig. 1, in red).

Episode-dependent connectivity of the sgACC

Individuals with rMDD exhibited amplified connectivity of the left sgACC to the right orbitofrontal cortex (OFC) and left hippocampus compared with aMDD, suggesting that weakened connectivity among aMDD may be an episode-dependent feature of illness.

Connectivity differences based upon number of episodes (burden)

Burden effects using the PCC seed—SE MDD exhibited a general pattern of weaker negative connectivity of the left PCC with a number of CCN regions including the bilateral IFG and MFG as well as the right inferior parietal lobule, relative to both HCs and ME MDDs (Fig. 2). Fig. 2 also illustrates increased positive connectivity in SE MDD of the left

PCC seed to the left MFG, relative to the HC and ME MDD groups. Table 3 details all significant group differences. All single *v.* multiple differences remained significant after covarying for age of first MDE.

Burden effects using the amygdala seed—Individuals with SE and ME MDD demonstrated relatively weakened connectivity of the left amygdala to the left cuneus compared with HCs, an effect independent of episode. Those with ME MDD exhibited weakened connectivity of the amygdala to the left inferior occipital lobe and right caudate head relative to HCs. Individuals with a SE MDD exhibited amplified connectivity of the amygdala with multiple frontal regions relative to those who had experienced multiple MDEs, especially in the medial frontal cortex, extending into orbital and subgenual cingulate regions, potentially reflecting the burden of multiple episodes (Fig. 2). In Table 3, connectivity values for half of the 10 seeds from the left amygdala to regions of relative hypoconnectivity were positively correlated with age of first MDE onset among individuals with multiple MDEs. All SE *v.* ME MDD differences remained after covarying for age for first MDE.

Burden effects using the sgACC seed—HCs and ME MDD exhibited greater connectivity of the left sgACC to the left middle occipital gyrus when compared with individuals with a SE MDD (Fig. 2). Individuals with ME MDD demonstrated increased connectivity to the right superior frontal gyrus (SFG) compared with HCs. Individuals with a SE MDD demonstrated amplified connectivity to the right IFG compared with ME MDD. The superior and inferior frontal results remained significant after covarying for age of first MDE, whereas the middle occipital finding was no longer significant.

Discussion

The diagnostic category of MDD remains a heterogeneous phenotype divided into poorly refined and largely overlapping subsets. The present study provides insight into how features of illness such as number of MDEs (burden) and phase of illness (episode-dependent *v.* independent) can be used to understand differences in resting-state data among young, unmedicated adults. Notable differences in connectivity were observed based upon in *v.* out of episode status. Further dissociations between individuals with varying longitudinal burden were observed when using a seed-based approach to probe the DMN and SN. Finally, effects in the SN and DMN with the CCN were observed in all MDD (episode-independent) relative to HCs. Specifically, all MDD demonstrated increased connectivity of the left amygdala with the right anterior insula, implicating an episode-independent abnormality within the SN. All MDD also demonstrated increased connectivity of the PCC to the right MFG, indicating that some DMN abnormalities are independent of acute MDE.

Episode-dependent and episode-independent differences in resting-state connectivity

Young adults in the remitted state demonstrated hyperconnectivity of the PCC with regions of the CCN, whereas individuals within an active episode demonstrated hyperconnectivity of the PCC with additional regions of the DMN and hypoconnectivity of the PCC with frontal regions of the CCN, consistent with the broader literature. Thus, using the PCC seed

results in divergent patterns within the DMN and between the DMN and CCN for the remitted *v.* active phases of illness suggesting they may be episode-dependent.

An additional notable episode-dependent effect of illness includes weakened connectivity of the sgACC to the OFC among participants with aMDD relative to rMDD. The left IFG appears to play an important role in the emotion regulation difficulties observed during acute illness including affective perception (Briceño *et al.* 2013). Individuals within an acute episode also exhibited enhanced connectivity within the DMN as well as from the amygdala to regions including the ipsilateral globus pallidus and putamen – also only in relation to the rMDD group. The globus pallidus and putamen are typically not described in the resting-state literature, although a recent study investigating basal ganglia connectivity in adolescent MDD found increased connectivity between striatal regions and portions of the CCN, DMN and SN (Gabbay *et al.* 2013). The observed episode-dependent effects suggest that more nuanced ascertainment criteria for studies of MDD may lead to greater homogeneity of results as well as unveil how patterns fluctuate across different phases of illness.

These specific findings extend and contextualize previous literature documenting abnormalities in connectivity between the DMN and CCN in MDD (Sheline *et al.* 2010; Kaiser *et al.* 2015) and suggest for the first time in a single study that hyperconnectivity of the DMN and SN with the CCN may be episode-independent. We specifically found that these abnormalities pertain to rMDD compared with both aMDD. This evidence indicates episodic features of illness (present only in one state, yet still different from HCs). It may also be an episode-independent feature predictive of disease course or perhaps even resilience. The SFG and MFG may represent an extension of the CCN that serves to down-regulate the DMN and SN among those who have recovered from MDD, perhaps representing an early compensatory response. Hyperconnectivity of frontal regions to the DMN in remitted individuals may be representative of increased cognitive control regulating the default mode, allowing these individuals to experience control over depressive symptoms such as rumination and negative internalizing states, allowing them to stay well over longer periods of time.

Burden differences in resting-state connectivity

Connectivity from the amygdala seed resulted in discrimination between MDD groups with single *v.* multiple episodes, independent of episode status, which has not frequently been examined in the literature to date. Traditional sample sizes have not allowed for nuanced examinations of the effect of a first-onset *v.* multiple episodes, which may contribute to the relative dearth of reported amygdala-based connectivity findings in MDD (i.e. only four of 25 studies used an amygdala seed in MDD; Kaiser *et al.* 2015). Specifically, in the present study the amygdala was hyperconnected to the bilateral ventral medial PFC among individuals with SE MDD compared with ME MDD and HCs. The amygdala was also hyperconnected with other regions of the SN in SE *v.* ME MDD, which may implicate a temporal decoupling of the amygdala from SN regions after the burden of ME MDD (Lee *et al.* 2012). In contrast, this was not evident in the comparison between SE MDDs and HCs, offering further evidence that the recurrence of illness may lead to disruption of SN function through decoupling. To date, a few studies have implicated decreased network coupling in

treatment-resistant depression (de Kwaasteniet *et al.* 2015; Dichter *et al.* 2015); however, our results suggest that this decoupling may occur much earlier in the course of recurrent MDD. Moreover, weakened connectivity between the left amygdala and right caudate among multiple MDEs compared with HCs indicates an effect of burden. The caudate is involved in reward and cognitive control and this hypoconnectivity among individuals with multiple episodes could relate to the anhedonic features often observed in treatment-resistant depression (Kerestes *et al.* 2012). Alternatively, the caudate also is known to perform subservient tasks within the CCN such as response inhibition (Aron *et al.* 2007; Langenecker *et al.* 2007). Collectively, these findings indicate that amygdala-based connectivity is worthy of examination among carefully selected depressed populations.

Interestingly, age of first onset was related to results deriving from the SE (typically hyper-) *v.* ME (typically hypo-) contrast. Upon closer examination, weakened connectivity was more readily observable among those with an earlier age of onset. It is possible that later onset of first MDE enables the CCN to develop more fully, and thus cross-network increases in connectivity are subsequently observed. It is also possible that early-onset MDE may relate to early trauma and increased number of episodes; some research examining early-life trauma suggests an adverse effect on development of the CCN (Rogosch *et al.* 1995; Majer *et al.* 2010; Spann *et al.* 2012) and may further affect relations of CCN to other networks. Furthermore, we do not know if there was enough time for later-onset MDD to develop multiple episodes to fully dissociate age of onset and number of episodes, or whether these differences may predate and predict the course of illness.

Limitations and future directions

We note several limitations of our study. First, the strict controls for movement resulted in a usable sample that was younger and less severe in symptomatology than the overall sample. These differences make the current results less generalizable. Second, the current data are cross-sectional and cannot discriminate between network abnormalities that render an individual vulnerable to the first onset of MDD, ME MDD, as opposed to a normal maturational process. To capture developmental trajectories that contribute to resiliency and risk in MDD, future longitudinal research could examine whether excessive coupling of intrinsic networks predicts first onsets of depression or relapse as adolescents transition into early adulthood. In addition, this study used retrospective interviews to capture illness and episode frequency, which may be biased by factors such as selective recall. Prospective studies of high-risk cohorts represent an important direction for future research. In addition, our stringent movement criteria resulted in the exclusion of a significant minority of the aMDD group which resulted in a modest group size; however, inclusion of these individuals would have resulted in different and potentially missed results (online Supplementary Fig. S1 illustrates those with movement obscure between-group effects). Our findings should be replicated with larger samples of individuals with aMDD. There were also differences in clinical demographics across sites. Furthermore, sex differences have been identified in previous research examining brain-based state and trait markers of illness (e.g. Versace *et al.* 2010). We controlled for sex but did not have adequate power to further analyse group × sex differences. Despite these limitations, we believe the current examination focused on a relatively early phase of illness provides a level of protection against potential confounds

including complex treatment histories or neural scarring, making the current study innovative and important. Last, our examination of burden of illness (single *v.* multiple episodes) deserves further exploration and replication as there were very few aMDD with a single episode. However, examination of bar graphs suggests that the result of ME MDD was prominent in both aMDD and rMDD.

In conclusion, this is the first resting-state fMRI study illustrating features of both active (in-episode) and remitted (out-of-episode) MDD highlighting future directions that can better define risk for illness onset as well as early course markers. Furthermore, hypoconnectivity previously attributed to recurrent, treatment-resistant MDD (e.g. burden) may be present much earlier in illness. The current results address an understudied, yet important set of questions regarding the dissociation of episode-related, compensatory and early scar features of multiple episodes of illness. Ultimately, distinguishing between individuals who are at increased risk for multiple episodes may guide practice parameters for maintenance treatment and secondary prevention efforts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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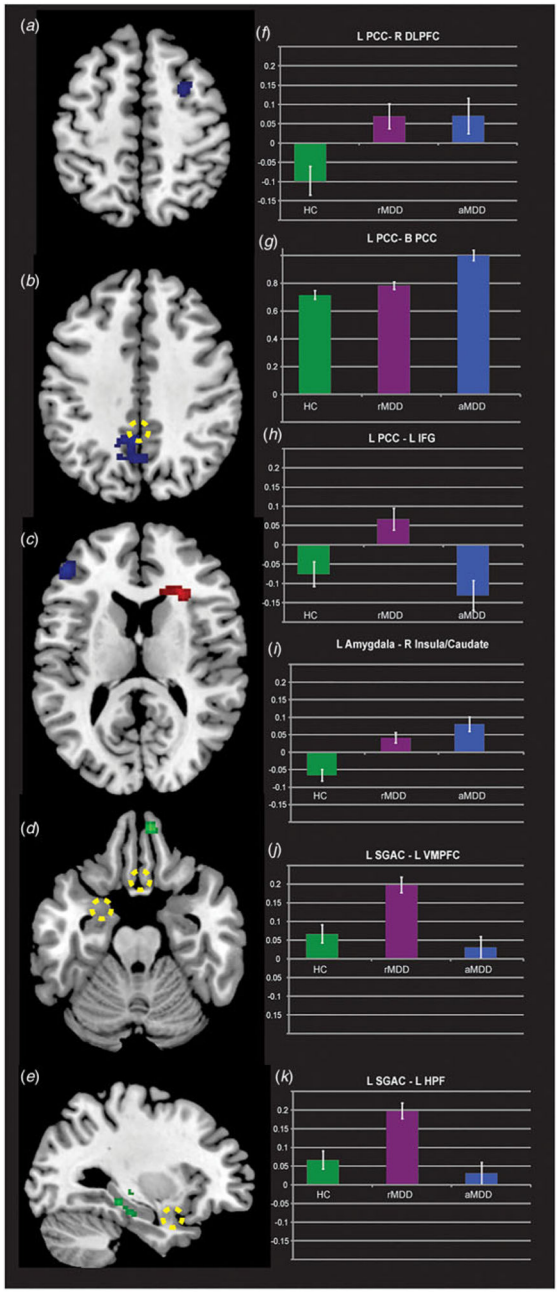

Fig. 1.

Differential connectivity between active and remitted major depressive disorder (aMDD and rMDD, respectively) compared with healthy controls (HC). Left (L) posterior cingulate cortex (PCC) seed probing default mode network connectivity highlighting differences between groups at the *F* test level (blue, panels *a*, *b* and *c* on the left and corresponding bar graphs on the right in panels *f*, *g* and *h*). Differences in amygdala connectivity based upon episodic state are illustrated at the *F* test level (panel *c* with extracted values in panel *i*). Subgenual anterior cingulate (SGAC) connectivity differences are also illustrated at the *F* test level (green, panels *d* and *e*, with corresponding extracted values in panels *j* and *k*).

Dashed yellow circles illustrate the locations of the PCC, amygdala and SGAC seeds. Views are axial for panels *a* to *d* and left sagittal for panel *e*. R, Right; DLPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus; VMPFC, ventromedial prefrontal cortex; HPF, hippocampal formation. Values are means, with standard errors represented by vertical bars.

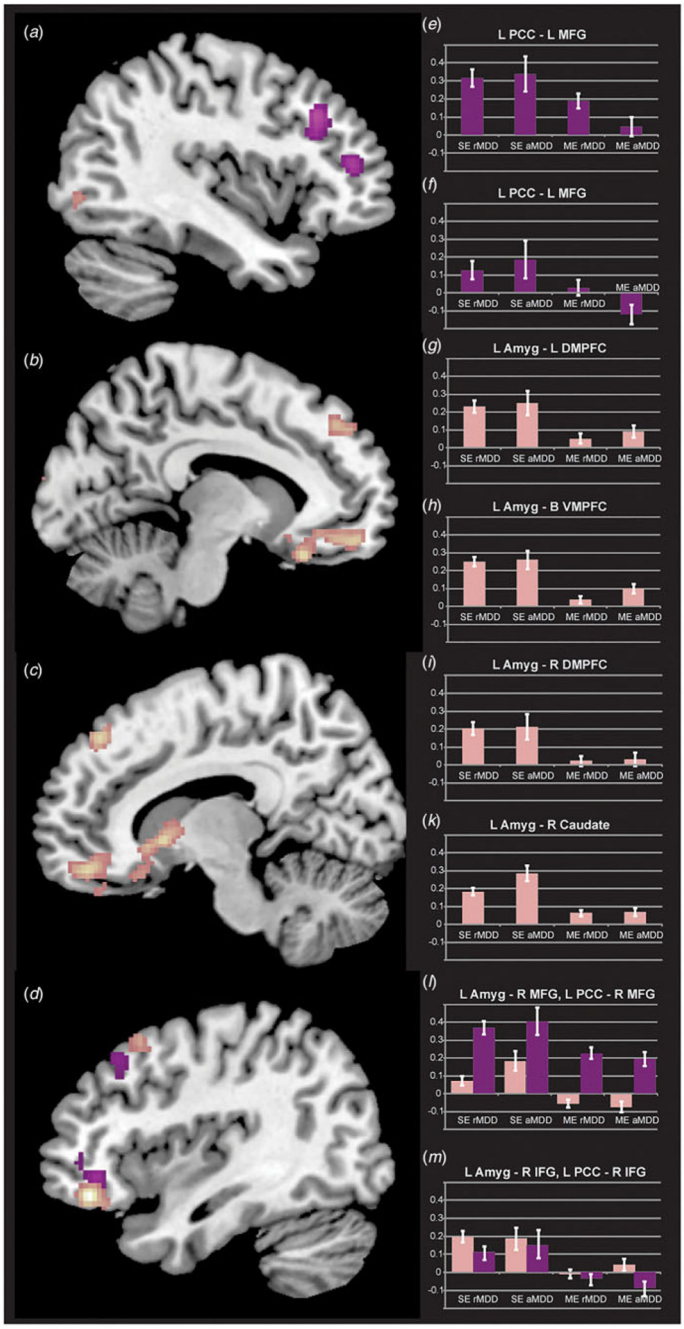

Fig. 2.

Differential connectivity between single-episode (SE) and multiple-episode (ME) major depressive disorder (MDD). Panels illustrate effects of burden in single episode *v*. multiple episode, further subdivided by in *v*. out of episode status (the latter provided to clarify that episode-linked and burden-linked effects are distinct). Views are sagittal for panels *a* and *b* (left) to *g* and *h* (right), and bar graphs generally align with the cluster from which they were extracted. Panel *a* (purple) indicates regions of decreased left (L) posterior cingulate cortex (PCC) connectivity in ME MDD relative to SE MDD in the left middle frontal gyrus (MFG;

also panels *c* and *d*). Decreased connectivity of the left amygdala (Amyg) in ME MDD was present and illustrated in the bilateral dorsomedial and ventromedial portions of the prefrontal cortex (DMPFC and VMPFC, respectively; panels *b* and *g*, pink, also panels *e*, *f* and *i*), and right caudate (panel *g*, also panel *k*). Panel *h* demonstrates decreased connectivity in ME MDD for the left PCC (purple) and left amygdala (pink) to closely linked middle frontal (MFG) and inferior frontal gyrus (IFG) regions, with these extracted data illustrated in panels l and m. rMDD, Remitted MDD; aMDD, active MDD; R, right; B, bilateral. Values are means, with standard errors represented by vertical bars.

Table 1

Demographic and clinic characteristics

	HC (*n* = 26)	rMDD (*n* = 34)	aMDD (*n* = 17)
Mean age*, years (S.D.)	21.15 (1.49)	21.06 (1.54)	22.35 (1.80)
Females, *n* (%)	14 (54)	25 (74)	11 (65)
Caucasian, *n* (%)	19 (76)	25 (74)	6 (67)
Mean education, years (S.D.)	14.84 (1.14)	14.41 (1.39)	14.69 (1.40)
Mean IQ estimate (S.D.)	106.9 (9.7)	108.4 (9.8)	110.5 (9.3)
Mean HAM-D* (S.D.)	0.35 (1.0)	2.35 (2.82)	18.65 (3.67)
History of co-morbid substance, *n* (%)	2 (8)	11 (32)	3 (18)
History of co-morbid anxiety*, *n* (%)	2 (8)	12 (35)	15 (88)
Past psychiatric medication*, *n* (%)	0	21 (62)	6 (36)
Mean number of MDEs* (S.D.)	N.A.	1.82 (1.21)	7.20 (8.88)
Mean age of first onset, years (S.D.)	N.A.	15.83 (3.09)	14.94 (4.02)
Site, *n*			
University of Michigan	17	17	10
University of Illinois at Chicago	9	17	7

HC, Healthy controls; rMDD, remitted major depressive disorder; aMDD, active major depressive disorder; S.D., standard deviation; IQ, intelligence quotient; HAM-D, Hamilton Rating Scale for Depression; MDEs, major depressive episodes; N.A., not applicable;

* $p < 0.05$.

Table 2

Group differences between active and remitted MDD compared with healthy controls using the PCC, amygdala and sgACC seeds

		MNI coordinates					
Contrast/lobe	**BA**	**x**	**y**	**z**	***Z***	**Cluster size, mm^3**	***Post-hoc* comparison**
Left PCC, *F* test group							
Frontal							
Inferior frontal	46	−46	42	12	4.20	592	rMDD > aMDD[a,b]*
Middle frontal	10	28	6	54	3.22	472	All MDD > HC
Limbic							
Posterior cingulate	31/7	−6	−50	36	4.34	2672	aMDD > rMDD[a]*
Left amygdala, *F* test group							
Subcortical							
Claustrum/insula	13	26	28	16	4.11	856	All MDD > HC
Left sgACC, *F* test group							
Frontal							
Orbital frontal	11	8	52	−24	3.97	536	rMDD > aMDD[a]*
Temporal							
Hippocampus		−32	−24	−4	3.47	528	rMDD > aMDD[a]*

MDD, Major depressive disorder; PCC, posterior cingulate cortex; sgACC, subgenual anterior cingulate cortex; BA, Brodmann's area; MNI, Montreal Neurological Institute; rMDD, remitted MDD; aMDD, active MDD; HC, healthy controls.

* $p < 0.05$, significantly correlated (within all MDD) with [a] the Hamilton Depression Scale and [b] age of first episode. No clusters are significantly correlated with the Hamilton Anxiety Scale.

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Table 3

Group differences between single and multiple major depressive episodes compared with healthy controls using the PCC, amygdala and sgACC as seeds

		MNI coordinates					
Contrast/lobe	**BA**	**x**	**y**	**z**	***Z***	**Cluster size, mm^3**	***Post-hoc* comparison**
Left PCC, *F* test group							
Frontal							
Middle frontal	9	−40	26	34	4.08	1440	Single > HC, multiple[a,b]
Middle frontal	9/46	28	24	36	3.33	1272	Single > HC, multiple
Inferior frontal	46	−44	42	12	3.9	936	Single > HC[a,b]
Inferior frontal	47/11	34	42	4	3.37	648	Single > HC, multiple[b]
Parietal							
Inferior parietal	22	52	−54	22	2.83	440	Single > multiple
Left amygdala, *F* test group							
Frontal							
Medial frontal	11	8	50	−16	4.13	7048	Single > HC, multiple[b]
Middle frontal	11	38	40	−14	4.72	1392	Single > multiple[b]
Middle frontal	6	42	18	52	3.54	1368	Single > multiple[b]
Superior frontal	8	12	40	48	3.85	1024	Single > multiple
Superior frontal	8	−8	50	40	3.57	752	Single > multiple
Limbic							
Uncus/amygdala	34	20	−4	−22	3.66	552	Single, multiple > HC
Temporal							
Inferior temporal	20	68	−26	−16	4	616	Single > multiple
Occipital							
Cuneus	18	−14	−98	18	3.48	608	HC > single, multiple
Inferior occipital	19	−38	−78	−2	3.42	504	HC > multiple[b]
Subcortical							
Caudate head		8	12	−2	3.86	1600	HC > multiple[b]
Left sgACC, *F* test group							
Frontal							
Superior frontal	10	20	64	20	3.61	1072	HC < multiple

		MNI coordinates					
Contrast/lobe	**BA**	**x**	**y**	**z**	***Z***	**Cluster size, mm^3**	***Post-hoc* comparison**
Inferior frontal	44/47	38	20	22	3.79	712	Single > multiple[b]
Occipital							
Middle occipital	18	−12	−98	22	3.98	528	HC, multiple > single[a]

PCC, Posterior cingulate cortex; sgACC, subgenual anterior cingulate cortex; BA, Brodmann's area; MNI, Montreal Neurological Institute; HC, healthy controls.

$^{*}p < 0.05$, within all major depressive disorder, significantly correlated with [a] the Hamilton Depression Scale and [b] age of first episode. No clusters are significantly correlated with the Hamilton Anxiety Scale.