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Altered patterns of central executive, default mode and salience network activity and connectivity are associated with current and future depression risk in two independent young adult samples

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Abstract

Neural markers of pathophysiological processes underlying the dimension of subsyndromal-syndromal-level depression severity can provide objective, biologically-informed targets for novel interventions to help prevent onset of depressive and other affective disorders in individuals with subsyndromal symptoms, and prevent worsening symptom severity in those with these disorders. Greater functional connectivity (FC) among the central executive network (CEN), supporting emotional regulation (ER) subcomponent processes such as working memory (WM), the default mode network (DMN), supporting self-related information processing, and the salience network (SN), is thought to interfere with cognitive functioning and predispose to depressive disorders. We examined in young adults: 1.relationships among activity and FC in these networks and current depression severity, using a paradigm designed to examine WM and ER capacity in n=90, age=21.7 (2.0); 2.the extent to which these relationships were specific to depression versus mania/hypomania; 3. whether findings in a first, “discovery” sample could be replicated in a second, independent, “test” sample of young adults n=96, age=21.6(2.1); and 4. whether such relationships also predicted depression at up to 12-months post scan and/or mania/hypomania severity in (n=61, including participants from both samples, age =21.6 (2.1)). We also examined the extent to which there were common depression- and anxiety-related findings, given that depression and anxiety are highly comorbid. In the discovery sample, current depression severity was robustly predicted by greater activity and greater positive functional connectivity among the CEN, DMN, and SN during working memory and emotional regulation tasks (all ps<0.05 qFDR). These findings were specific to depression, replicated in the independent sample, predicted future depression severity. Similar neural marker-anxiety relationships were shown, with robust DMN-SN FC relationships. These

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Author Contributions

MAB, YA-A, and MLP conceived of and wrote the manuscript; MAB, YA-A, and RR completed the analyses; MAB, YA-A, RR, SI, and MLP conceived of and interpreted the statistical analysis; RS, HA, and GB contributed substantially to the acquisition of the data. All authors mad significant contributions to the manuscript and all approved the final version.

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data help provide objective, neural marker targets to better guide and monitor early interventions in young adults at risk for, or those with established, depressive and other affective disorders.

Introduction

Almost one-fifth of all 18-25 year-olds seek help from mental health professionals for emotional distress[1], including the range of subsyndromal depression severity. These symptoms can develop into, and thus represent a dimension of psychopathology that confers risk for, depressive and/or other affective disorders[2]. Identifying neural markers of pathophysiological processes underlying the full dimension of low subsyndromal to syndromal level depression severity can provide objective, biologically-informed targets to guide treatment choice and targeting of novel interventions to help prevent future onset of these disorders in individuals with subsyndromal symptoms and behaviors, and worsening depression severity in those with these disorders. This approach accords with the NIMH Research Domain Criteria [3] focus on conceptualizing psychiatric illness in terms of dimensions of dysfunction in neurobiological systems to obtain a better understanding of illness mechanisms, rather than focusing only on individuals with fully syndromal-level symptoms and categorically-defined disorders. This approach is especially important in young adulthood, not only because of the high incidence of affective disorders during this age range[1], but also because the effectiveness of interventions can be maximized by taking advantage of neurodevelopment during this developmental period [4–6].

Working memory (WM) deficits [7–9] and emotional dysregulation[10–13] are associated with present and future[14, 15] affective psychopathology, especially depression[7, 11, 16], and thus are important processes on which to focus in studies aiming to identify neural markers of future affective disorder risk in young adults. It is well established that largescale neural networks play important roles in these processes. These neural networks include, in particular, the central executive network (CEN)/frontoparietal network (FPN)[17–19], the default mode network (DMN)[20, 21], and the salience network (SN) [22, 23]. The CEN supports WM, decision-making and problem solving subprocesses important for emotional regulation (ER), and is centered on the dorsolateral prefrontal cortex (dlPFC), and lateral posterior parietal cortex (lPPC), thalamus and caudate [24, 25]. The DMN supports self-referential processing and introspection, and is centered on the posterior cingulate cortex (PCC), precuneus, medial prefrontal cortex(mPFC), and inferior parietal cortex[26–28]. The SN detects and integrates salient, i.e., interoceptive and emotional information, and is centered on the dorsal anterior cingulate cortex (dACC) and anterior insula, and also includes subcortical regions such as the amygdala that are important for emotion processing [24].

DMN deactivation [29, 30] alongside greater CEN activity and inverse FC (anticorrelation) between the CEN and DMN in adults [31, 32] and youth[33, 34] during executive function, e.g. WM, tasks important for ER[32], is thought to reduce interference from self-monitoring processes on cognitive task performance [31, 35–37] (although see[38]). By contrast, greater DMN activity[39–41] during task activity and rest is associated with greater depression severity [42]. In addition, aberrant positive CEN-DMN functional connectivity (FC) is associated with ER deficits in preschool and school-age children [43] and with worsening depression

severity in school aged children and adolescents at familial risk for affective disorders[44]. Other studies reported that lower CEN and DMN anticorrelation during tasks or at rest is associated with greater current and future depression[40, 45, 46 47] and non-suicidal self-injurious behavior in youth [48]. The SN, and dACC in particular, supports switching between the DMN and CEN [49], with an increasing number of studies reporting abnormally elevated SN FC with the CEN and/or DMN in depressed individuals, especially during rest[48, 50–53], although there are some reports of relationships between lower FC among all three networks and depression[54]. These findings support the triple network model of affective disorders, where dysfunction in one network impacts the other networks[24]; yet, it remains unclear how activity and FC within and among these three neural networks, specifically during WM and ER tasks, are associated with current and future depression severity in young adults.

It is also unclear whether the above relationships are specific to depressive symptom severity or common to a broader range of affective symptoms, including mania/hypomania, in young adults, as few studies included measures of both mania and depressive symptom severity in analyses of relationships among CEN, DMN and SN activity and FC and affective symptoms in this age group. Our previous study in youth indicated that the relationship between CEN-DMN FC and depressive symptom severity was specific to depression and not common to mania/hypomania[44], but more studies are needed for confirmation. Furthermore, given that depression and anxiety are highly comorbid [55, 56], examining the extent of overlap among neural network activity and FC associated with depression versus anxiety will determine whether these neural markers reflect distinct pathophysiological processes underlying each symptom dimension, or a process common to both dimensions. There is also a critical need to replicate neuroimaging findings in independent and larger samples[57–59] to provide robust neural markers of pathophysiological processes.

In the present study, our overarching goal was thus to identify, in young adults, relationships among current depressive symptom severity and activity and FC within and among the CEN, DMN and SN during a paradigm designed to examine WM and ER capacity. Two independent samples of young adults were recruited across a range of depressive symptoms, from healthy to subsyndromal to fully syndromal. First, we aimed to examine relationships among activity within and FC among the CEN, DMN and SN and depressive symptoms in the first, “discovery” young adult sample, and then determine the extent to which these findings could be replicated in an independent, “test” young adult sample. We then aimed to determine the extent to which those neural measures associated with current depressive symptom severity also predicted future depressive symptom severity up to one year later in the combined sample of young adults who had follow-up clinical assessments. We used mania symptom severity as a comparison measure to determine whether CEN, DMN and SN activity and FC-depressive symptom severity relationships were specific to depression or related to a broader range of affective symptoms. Our hypotheses were fourfold:1.In the Discovery sample, greater DMN and SN activity, and FC among the three neural networks during WM and ER task performance would be associated with greater current depressive symptom severity; 2.These relationships would be specific to depressive symptom severity and not common to mania; 3.These patterns would be replicated in the independent sample of young adults; 4.These patterns would also predict future depressive symptom severity. We

further examined the extent to which these patterns of activity and FC were also associated with current and future anxiety.

Methods

Participants

Participants were two independent samples of young adults recruited across a range of subsyndromal to syndromal depression.

Discovery sample: n=133 young adults were scanned on a Siemens Trio scanner (supplement); n=43 were removed due to: missing data (n=25), failure to successfully complete the task (n=1), excessive motion (>4 mm or mean framewise displacement >.5), signal loss, and/or severe artifacts in their neuroimaging data(n=17). The final sample was n=90,age=21.7(2.0); n=36 individuals were seeking help for psychological distress and n=54 individuals were healthy with no previous personal or family history of psychiatric illness. The sample thus provided a range of depressive and mania/hypomania severity (Table 1).

Independent *Test sample*:n=136 young adults were scanned on a Siemens Prisma scanner (supplement) n=40 were removed due to: missing data(n=11), excessive motion (as above) (n=29). The final sample was n=96, age=21.6(2.1); n=54 were individuals seeking help for psychological distress and n=42 were healthy.

Harmonized sample to predict future affective symptom severity:n=61distressed young adults from both the *Discovery* and *Test* samples with up to 12-months of follow-up clinical data; n=45 female, age=21.2(2.1).

Participants were recruited via advertisement, student counseling services, and participant registry. The University of Pittsburgh Human Research Protection Office approved the study. All participants provided informed consent.

Clinical Measures

Participants were assessed on several clinical measures(supplement). The focus of the analyses were depression, assessed using the Hamilton Rating Scale for DepressionHAM-D; [60], anxiety, assessed using the Hamilton Rating Scale for Anxiety[61], and mania, assessed using the Young Mania Rating Scale[62]. Table 1 for relationships among clinical measures.

Exclusion criteria—Exclusion criteria were: history of head injury, neurological, pervasive developmental disorder or systemic medical disease (from medical records and report by each potential participant); cognitive impairment (Mini-Mental State Examination [63] score<24, and premorbid NAART IQ [64] estimate<85; visual disturbance (<20/40 Snellen visual acuity); left or mixed handedness (Annett criteria [65]); alcohol/substance abuse/ dependence (including nicotine) and/or illicit substance use (except cannabis) over the last 3 months, determined by Structured Clinical Interview for DSM-5 (SCID) [66] (and psychiatric records, if available). Lifetime/present cannabis use (non-abuse levels) was allowed, given its common usage in 18-25 year-olds [67]. Urine tests on the scanning day excluded individuals with current illicit substance use (except cannabis); salivary alcohol

tests excluded individuals who were intoxicated on the scanning day. Additional exclusion criteria were MRI screening criteria, positive pregnancy test or self-reporting of pregnancy for females; and taking any psychotropic medication or medication combination for >2 weeks, and/or having fewer than 3 months between starting any present psychotropic medication and stopping previous psychotropic medications. A history of seeking help for psychological distress, e.g., any emotional, behavioral or substance abuse/dependence problems, irrespective of having received a DSM diagnosis or not, was allowed in distressed individuals, as long as psychotropic medication stipulations were met as above.

Neuroimaging data acquisition—Functional neuroimaging data were collected using a 3.0 Tesla Siemens Trio 2 MRI scanner in the Magnetic Resonance Research Center (MRRC) at the University of Pittsburgh Medical Center. A total of 504 blood-oxygenation-level-dependent (BOLD) images were acquired with a simultaneous multi-slice (SMS) gradient echo EPI sequence (18 slices, SMS factor=3, TR=1500, TE=30 ms, Field of View (FOV)=220 × 220 mm, matrix=96 × 96, Flip Angle=55°, Bandwidth= 1860 Hz/Px). In addition, we acquired structural 3D axial MPRAGE images (TR=1500 ms, TE=3.19 ms, Flip Angle 8°, FOV=256 × 256 mm, 1 mm isotropic voxels, 176 continuous slices), and fieldmaps (TR=500 ms, TE1=4.92 ms, TE2=7.38 ms, FOV=220 × 220 mm, matrix=96 × 96, Flip Angle=45°, Bandwidth=1302 Hz/Px).

Functional Imaging task—The emotional n-back (EFNBACK) task is a modified version of the n-back WM task [68], and has been employed previously in studies of youth and adults to examine neural networks supporting WM and the ability to redirect attention away from emotional distracters, a key component of ER [13, 69–71]. The EFNBACK task consists of visually presenting a pseudorandom sequence of letters with participants responding to a pre-specified letter. The n-back task includes two memory load conditions: a low-memory load (0-back-e.g., press the button to “M”) and high memory load (2-back-e.g., press the button whenever the letter is identical to the letter presented two trials back (L-X-L)); each memory load condition includes one of four emotional face distractor conditions (fearful, happy, neutral, or no face distractor). The task comprises three, 7-min 4-sec runs, for a total of 24 blocks. Each block includes 12 trials. Trial duration is 500ms. The inter-trial interval comprises a fixation cross (flanked with faces), and is jittered (mean duration=3500ms). Participants respond as quickly as possible with their index finger to the target letter. Brief instructions are presented on the screen for 4000ms at the beginning of each block. Detailed instructions are provided during task practice prior to the scanning session. Incorrect trials were excluded from the analysis.

Power calculation

With our sample sizes (n=90 and n=96) for continuous outcome measures, we have 79%-91% power, respectively, to detect a significant (p=0.05) effect (effect sizes:f2=0.15) for a the independent variables, controlling for up to 5 predictor variables.

Supplement for fMRI processing details.

Activity

Models were constructed to examine WM:2-backWM *without* face distractors versus 0-backWM *without* distractors contrast (2-backWM>0-backWM); and redirection of attention away from emotional distracters during WM, ER:2-backWM *with* emotional face distractors versus the 0-backWM *without* distractors contrast (2-backER>0-backWM). We used a single anatomical mask, created from the WFU PickAtlas Wake Forest University, Winston-Salem; [72]. The mask included regions within the CEN (dlPFC [Brodmann Areas (BA)9 and 46] and caudate), DMN (precuneus [BA7]), and SN (amygdala, dACC [BA24/32]). A cluster forming threshold FWE corrected, p=0.05, k>10 was used.

Functional connectivity

Generalized psychophysiological interaction (gPPI; [73] was used to examine FC between anatomical seed regions in the CEN (bilateral dlPFC), DMN (bilateral precuneus), and SN (bilateral dACC) for both WM and ER. For ER, we used an additional bilateral amygdala seed region(anatomically-defined, using WFUPickAtlas), given the key role of this region in emotion processing[74]. The target ROI mask is defined above. A cluster forming threshold FWE corrected, p=0.05, k>10was used.

EFNBACK task accuracy

Task accuracy of >70% correct was used, as in previous studies[44].

Data analytic plan

The following steps were included:

Step-1. In the *Discovery sample* and the *Test sample*, we identified regions showing significant activity and FC in the mask to 2-backWM>0-backWM and 2-backER>0-backWM across participants in SPM. We extracted parameter estimates of activity and FC to these contrasts.

Step-2. For each dependent variable (DV) (current depression and mania) we tested the assumptions of linear regression to identify the appropriate regression model to use.

Step-3. *Discovery sample*: To test Hypotheses 1and 2, we used elastic-net penalized least squares regression analysis for variable selection with the GLMNET package in R[75] and the appropriate regression family to assess 4 models: 1.WM-contrast-related significant neural activity and FC (from Step-1) along with demographic variables were independent variables (IVs), and current depression severity was the DV; 2.WM-contrast-related significant neural activity and FC (from Step-1) along with demographic variables were IVs, and current mania/hypomania severity was the DV; 3.ER-contrast-related significant neural activity and FC (from Step-1) along with demographic variables were IVs, and current depression severity was the DV; 4.ER-contrast-related significant neural activity and FC (from Step-1) along with demographic variables were IVs, and current mania/hypomania severity was the DV. Λ.1se was selected as a more conservative model in which more coefficients are set to zero.

Step-4. *Discovery sample*: Using SPSS, we then examined the extent to which the measures of WM and ER contrast-related neural network activity and FC that were identified in Step-3 were associated with each DV in each of the four IV-DV models, using the appropriate regression family. A Benjamini-Hochberg FDR adjusted p-value <.05 was used to correct for multiple comparisons within each model and across models within samples.

Step-5. The patterns of contrast-related significant neural activity and FC observed in the *Test sample* were mostly consistent with that shown in the *Discovery sample*, which allowed the models generated in Step-4 to be tested for replication in the independent sample. To test Hypothesis 3, we examined the extent to which WM-contrast-related IVs identified in Step-4 were significantly related to DVs (current depression or mania) and the extent to which ER-contrast-related IVs were significantly related to DVs (current depression or mania) in this independent sample of young adults. We assessed replication of the model performance using standard CV [76]. This is a comparison of the average in-sample and out-of-sample difference between predicted depression score and actual depression score. Formula: average(abs(log(actual depression score)-predicted depression score)).

Step-6. *Harmonized sample*: To test Hypothesis 4, using Combat[77] to control for scanner effects, we harmonized the data for participants who had 6-12 months' follow up DV data (i.e., future depression or mania severity) from the *Discovery sample* and the *Test sample*. Using SPSS and the appropriate regression family, we examined the extent to which the identified harmonized IVs from Step-4, along with time between scan and follow up, were related to DVs.

Step-7. We completed post hoc sensitivity tests of Step-4 and Step-5 in subsets of participants who 1. were not taking medication; 2. who did not have a diagnosis of depression, anxiety, or bipolar disorder; and 3. of Step-6 *Harmonized sample*, testing change over time in medication, age, gender, and IQ (supplement).

Step-8. Step-4-Step-6 were completed with current/future anxiety as the DV.

Results

Task accuracy

Discovery sample: task accuracy mean(SD)=0.98(.02), *Test sample*: task accuracy mean=0.97(.03).

Step-1. We showed consistent patterns of CEN (dlPFC), SN (dACC) and DMN (precuneus) activity and FC during 2-backWM>0-backWM and consistent patterns of CEN (dlPFC), SN (dACC) and DMN (precuneus) activity and FC during 2-backER>0-backWM across participants in both the *Discovery sample* and *Test sample*(*Table* 2, Supplemental figures 1–4).

Step-2. The residuals of the DVs showed non-normal distributions with a positive skew. Additionally, the standard deviations of the DVs were larger than the means, suggesting overdispersion. Given these characteristics, and the nonnegative count nature of the scores, we used negative binomial regression models for all analyses[78]. The negative binomial

model is an extension of Poisson regression to be used to improve standard errors and test statistics in overdispersed models [79].

Step-3. *Discovery sample WM*: elastic net variable selection after CV identified left dlPFC activity, right precuneus activity, and bilateral dlPFC-right dACC FC to the 2-backWM>0-backWM contrast as measures associated with current depression severity.

Discovery sample ER: elastic net variable selection after CV identified left dlPFC activity, left dACC activity, right precuneus activity, bilateral precuneus-left dACC FC, bilateral precuneus-right dlPFC FC and bilateral dlPFC-right dACC FC to the 2-backER>0-backWM contrast as measures associated with current depression severity.

Discovery sample: Neither WM and ER contrast-related neural activity and FC nor demographic variables were associated with current mania/hypomania severity in the negative binomial elastic-net model after CV; thus, no additional tests with mania/hypomania were completed.

Step-4. *Discovery sample WM*: a negative binomial regression model revealed that left dlPFC activity (Odds Ratio (OR):1.80, CI:1.42-2.28, qFDR<0.001), right precuneus activity (OR:1.43, CI:1.12-1.82, qFDR=0.004), and bilateral dlPFC-right dACC positive FC (OR:1.75, CI=1.44-2.13, qFDR<0.001) to 2-backWM>0-backWM were positively associated with current depression severity (Table 3, Figure 1a–b).

Discovery sample ER: a negative binomial regression model revealed that left dlPFC activity (OR:4.27, CI:2.09-8.72, qFDR<0.001), bilateral precuneus-left dACC positive FC (OR:1.64, CI:1.06-2.53, qFDR=0.046), bilateral precuneus-right dlPFC positive FC (OR:1.67, CI:1.22-2.29, qFDR=0.007), and bilateral dlPFC-right dACC positive FC (OR:1.49, CI:1.09-2.04, qFDR=0.028) to 2-backER>0-backWM were positively associated with current depression severity (Table 3, Figure 1g–i).

Step-5. *Test sample WM:* a negative binomial regression model revealed that left dlPFC activity (OR:2.90, CI:2.31-3.64, qFDR<0.001) and right precuneus activity (OR:1.88, CI:1.54-2.29, qFDR<0.001) to 2-backWM>0-backWM were positively associated with current depression severity (Table 4, Figure 1 c–d). dlPFC-dACC FC was not observed in the *Test sample*, and thus was not included in the model (Table 2).

Test sample ER: a negative binomial regression model revealed that left dlPFC activity (OR:2.65, CI:1.94-3.63, qFDR<0.001), bilateral precuneus-left dACC positive FC (OR:11.22, CI:7.26-17.34, qFDR<0.001) and bilateral dlPFC-right dACC positive FC (OR:2.61, CI:1.89-3.60, qFDR<0.001) to 2-backER>0-backWM were positively associated with current depression severity (Table 4, Figure 1 j–l). Bilateral precuneus-right dlPFC FC was not observed in the *Test sample*, and thus was not included in the model (Table 2).

Step-6. *Harmonized sample WM:* a negative binomial regression model revealed that left dlPFC activity (OR:2.81, CI:2.21-3.56, qFDR<0.001), and right precuneus activity (OR:1.49, CI:1.21-1.85, qFDR<0.001) to 2-backWM>0-backWM were positively associated with future depression severity. Days between scan and follow up was not significantly

related to future depression severity (p=0.537) (Table 5, Figure 1e–f).*Harmonized sample ER: a* negative binomial regression revealed that left dlPFC activity (OR:3.55, CI:2.52-5.00, qFDR<0.001), bilateral precuneus-left dACC positive FC (OR:6.26, CI:3.62-10.53, qFDR<0.001), and bilateral dlPFC-right dACC positive FC (OR:3.65, CI:2.34-5.68, qFDR<0.001) to 2-backER>0backWM were positively associated with future depression severity. Days between scan and follow up p=0.245 was not related to future depression severity (Table 5, Figure 1m–o). Testing all seven neural measures in one binomial regression model in the Harmonized sample showed consistent positive relationships between future depression severity and DMN activity to WM, CEN activity to ER along with DMN-SN and CEN-SN FC to ER (Supplemental table 5 c).

Step-7. The same patterns of relationships were also shown in unmedicated individuals, and individuals without current mood or anxiety disorders (Supplemental tables 1–4).

Step-8. The same patterns of CEN and DMN activity during WM (all ps<0.004); and of CEN activity and DMN-SN FC (all ps<0.005) were associated with current and future anxiety in the Discovery and Test samples, however, during ER, anxiety severity showed an additional relationship with DMN activity (ps<0.026) and no CEN-related FC (p=0.094) (Supplemental tables 6–7).

Standard CV for depression showed similar predictive performance for WM: Discovery sample=1.13 and Test sample=0.70; ER: Discovery sample=1.27, Test sample=0.60. *Standard CV* for anxiety showed similar predictive performance for WM: Discovery sample=0.89 and Test sample=0.54; ER: Discovery sample=1.00, Test sample=0.75.

Discussion

In young adults recruited across a range of subsyndromal-syndromal depressive symptom severity, both current and future depression severity were predicted by patterns of activity and FC among the CEN, SN, and DMN, and replicated in an independent sample. Specifically, in two independent samples during WM, current and future depression and anxiety severity were positively associated with left dlPFC and right precuneus activity. In these two samples during ER, current and future depression severity were positively associated with left dlPFC activity, along with DMN-SN and CEN-SN FC. These findings were related to depression, were partially related to anxiety, were not common to mania/hypomania, and support our hypotheses emphasizing triple network[24] dysfunction as a pathophysiological process underlying depression in young adulthood. These results also suggest common and distinct triple network dysfunction related to the psychopathology of depression and anxiety.

Regarding WM, our finding in the Discovery sample that greater activity in key regions of the CEN (dlPFC) and DMN (precuneus), along with greater bilateral dlPFC-right dACC FC, were associated with greater current depression/anxiety severity suggests that greater involvement of DMN-related introspection and self-referential thought processes[26–29] might have necessitated greater recruitment of the CEN dlPFC and greater influence of the SN on the CEN to successfully complete the WM task. The dlPFC and precuneus relationship

findings were replicated in the Test sample, indicating that this pattern of activity during WM is an especially robust marker of depression/anxiety severity in young adulthood.

During ER, there was a more widespread pattern in the Discovery sample of positive relationships between current depression severity and activity in the CEN left dlPFC, along with positive FC between regions in all three networks, including precuneus-dACC FC, precuneus-dlPFC FC and dlPFC-dACC FC. These measures of CEN activity and positive FC between the DMN and SN and between the CEN and SN were replicated in the Test sample. These findings in particular support the triple network model[24], where greater dlPFC activity along with higher FC between the DMN and SN and between the SN and CEN were associated with greater current depression severity. The SN is thought to modulate the extent of anticorrelation between the DMN and CEN [80]; and the dACC in particular is thought to be important for CEN engagement and DMN disengagement[49] to allow switching between monitoring internal states and cognitive or behavioral control in response to external stimuli [49]. The positive relationships among current depression severity and CEN activity, CEN and DMN positive FC with the SN dACC therefore suggest that greater positive FC between the DMN and SN might facilitate greater engagement of the DMN during ER, necessitating a compensatory increase in FC between the SN and CEN, and CEN activity. Greater current and future anxiety severity were also associated with greater dlPFC along with higher DMN-SN FC, but additionally by greater precuneus activity and not by dlPFC-centered FC, during ER. These findings suggest largely common, but also some distinct, pathophysiological mechanisms underlying depression and anxiety during ER, possibly reflecting a higher level of DMN-centered self-referential thought processes and lower disruption of CEN-related executive function underlying anxiety than depression.

Together, these results support previous findings linking greater involvement of the DMN and compensatory increase in CEN activity during cognitive task performance with current depression/anxiety severity[40, 44–46], and relationships between a failure to deactivate DMN regions during challenging cognitive tasks and greater future depression/anxiety in youth at risk for affective disorders[44, 46]. Our findings also parallel those of other studies showing lower levels of DMN deactivation during executive task performance in individuals with affective and anxiety disorders, including depression and bipolar disorder[81–89]. Additionally, the positive association between DMN-SN positive FC and depression severity parallels previous work linking DMN-SN FC during an emotional Stroop task with depression[52]. The relationships between depression/anxiety severity and left dlPFC activity concord with previous findings of elevated left dlPFC during WM and ER tasks in depressed and anxious individuals[90–93], possibly reflecting the role of the left hemisphere in language in right handed individuals[94], given that both WM and ER tasks involved encoding and memory of letters. The laterality of the DMN and SN activity and FC measures showing relationships with depression/anxiety severity was less consistent across samples, however, concurring with a recent meta-analysis that reported inconsistent patterns of laterality in wholebrain regional associations with depression and anxiety [95]. Interestingly, future depression was predicted more by ER-related than by WM-related activity and FC; suggesting greater importance of ER than WM contexts on the ability of dysfunctional patterns of neural network interactions to predict future depression.

Our findings were specific to depression/anxiety and there were no identified measures related to mania/hypomania. This finding highlights the key role of aberrant functioning within largescale networks during WM in depression [83], and suggest that other processes such as reward dysfunction might underlie development of mania/hypomania [96–98]. Amygdala activity and FC were not associated with current depression/anxiety severity during ER. This might reflect the fact that only participants who successfully redirected attention away from emotional face distracters during ER were included in analyses, as it would have been challenging to interpret neuroimaging findings in participants who were unable to perform the ER task.

The above neural network activity FC were also positively associated with future depression/anxiety severity, indicating that these measures likely reflected a pattern of neural network and associated cognitive functioning capacity that was associated with future depression/anxiety risk. Furthermore, these findings survived after including as covariates medication over the follow-up period, age, gender and IQ (Supplement Table5). Interestingly, age, gender, and IQ in the Discovery sample elastic net models were not associated with current depression/anxiety severity, suggesting that neural markers reflecting underlying pathophysiological processes more than demographic measures are important predictive markers of current depression/anxiety severity.

There were some limitations to the present study. Not all activity and FC shown to be significant at FWE correction in the *Discovery sample* was also significant in the *Test sample* (Step-1). This might reflect sample characteristics or scanner acquisition parameters. We chose to use the most robust activity and FC available from the data to include the most important neural measures. The majority of participants were able to perform the task with high accuracy levels. Inclusion of more challenging ER and WM tasks would lead to a greater range of performance accuracy and allow examination of relationships among pattens of neural network activity and FC and task performance. Two *Discovery sample* participants and three *Test sample* participants were medicated, and some participants had a diagnosis at baseline. Sensitivity analyses showed no impact of these characteristics on the relationships between neural activity and current and future depression severity (Supplemental Tables 1–4). Our study included a naturalistic follow up, allowing examination of vulnerability to future affective disorders. Future, intervention-based studies can determine the extent to which these neural measures can be used to monitor the effectiveness of the interventions[99–101]. We focused on depression/anxiety and mania/hypomania as they are the principal affective measures, although the range of mania/hypomania symptom severity was small. Future studies can examine BD at risk samples in whom a wider range of subsyndromal mania/hypomania is observed[102]. We adopted a dimensional approach to symptoms without a categorized control group, which allowed us to examine relationships across a range of symptoms.

We show in two independent samples with similar predictive performance that greater current and future depression/anxiety severity are positively associated with greater activity in and FC among regions comprising in the CEN, SN, and DMN. These findings highlight triple network [24] dysfunction as a pathophysiological process underlying depression/anxiety in young adulthood, and provide neural markers to help guide and monitor interventions to

help delay or prevent onset of depressive disorders or worsening of depression and anxiety in those already diagnosed with these disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Conflict of Interest:

The authors declare no conflict of interest. This work was supported by R37MH100041 (Phillips) from the National Institute of Mental Health, the Pittsburgh Foundation (PI: Phillips), and the Brain and Behavior Research Foundation (PI: Bertocci). The funding sources exerted no influence over the work.

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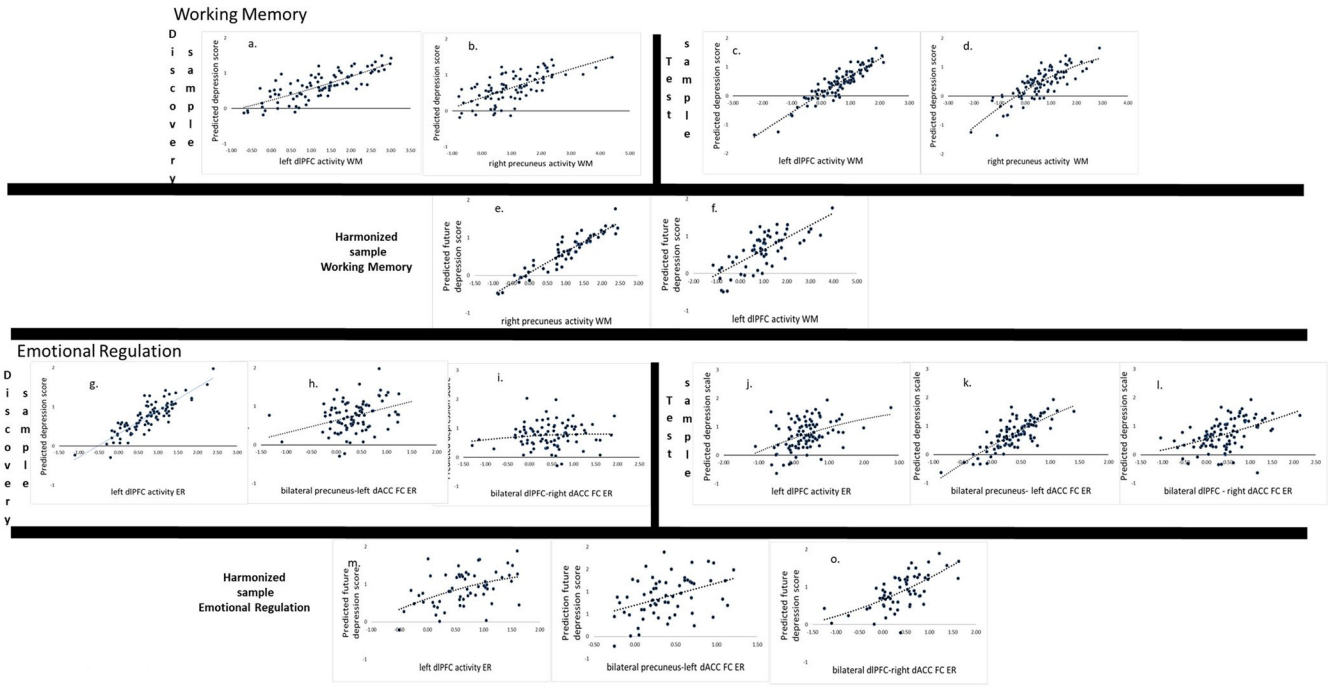

Figure 1. Prediction of depression scores from neural makers.

Discovery sample: working memory activity prediction of current depression score from **a**. left dlPFC WM activity; **b**. right precuneus WM activity; Test sample: working memory activity prediction of current depression score from **c**. left dlPFC WM activity; **d**. right precuneus WM activity; Harmonized sample: working memory activity prediction of future depression score from; **e**. left dlPFC WM activity; **f**. right precuneus WM activity; Discovery sample: emotional regulation activity and functional connectivity prediction of current depression score from **g.** left dlPFC activity; **h.** bilateral precuneus-left dACC ER FC; **i**. bilateral dlPFC-right dACC ER FC; Testing sample: emotional regulation activity and functional connectivity prediction of current depression score from **j.** left dlPFC activity; **k.** bilateral precuneus-left dACC ER FC; **l**. bilateral dlPFC-right dACC ER FC; Harmonized sample: emotional regulation activity and functional connectivity prediction of future depression score from **m.** left dlPFC activity; **n.** bilateral precuneus-left dACC ER FC; **o**. bilateral dlPFC-right dACC ER FC. Abbreviations: dorsolateral prefrontal cortex (dlPFC), dorsal anterior cingulate cortex (dACC), working memory (WM), emotional regulation (ER), functional connectivity (FC).

Table 1.

Clinical and demographic data of the two samples. Abbreviations: Young Mania Rating Scale (mania); Hamilton Depression Scale (depression); Hamilton Anxiety Scale (anxiety). Mean (standard deviation) or n (percentage) reported as appropriate.

	Discovery sample (n=90)		Test sample (n=96)		Statistics	P-value
Age (years)	21.73 (2.02)		21.56 (2.10)		t(184)=0.559	0.577
Gender (Female)	60		65		X^2 = .23	0.88
Group (Distressed)	35 (38.8%)		54 (56.3%)		X^2 = 4.94	0.026
Education					X^2=5.35	0.539
Partial high school	0		1			
High school diploma or General Equivalency Degree (GED)	14		13			
Some college (at least one year)	53		53			
Technical school or Associates Degree	0		2			
College diploma (Bachelor's Degree)	21		22			
Graduate or Professional Degree	2		5			
IQ	108.90 (6.88)		108.70 (6.57)		t(184)=0.20	0.84
Diagnosis						
Current depression	11 (12.2%)		16 (16.7%)		X^2=.425	0.515
Current bipolar disorder	0 (0%)		2 (0.02%)			
Current anxiety disorder	17 (18.8%)		38 (39.6%)		X^2=8.58	0.002
Clinical measures						
	Dx (n=21)	No Dx (n = 69)	Dx (n=40)	No Dx (n=56)		
mania	3.48 (2.23)	0.65 (1.28)	2.55(1.85)	0.77(1.55)	t(184)=−0.71	0.48
depression	18 (6.34)	3.12(5.38)	14.6(6.23)	4.38(6.09)	t(184)=−1.70	0.09
anxiety	15.52 (5.98)	2.17(3.88)	12.33(5.38)	2.93(4.26)	t(184)=−1.53	0.127
Correlatations						
depression and anxiety	r= .955 p<.001		r=.951, p<.001			
depression and mania	r= .757, p<.001		r=.621, p<.001			
anxiety and mania	r=.796, p<.001		r=.616, p<.001			
Psychotropic medication use (yes)	2 (0.02%)		3 (0.03%)			

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Table 2.

Results of Step 2. Significant contrast related activity and functional connectivity. WM contrast is 2backWM>0backWM. ER contrast is 2backER>0backWM. Abbreviations. WM = working memory, ER=emotional regulation, dlPFC= dorsolateral prefronal cortex, dACC= dorsal anterior cingulate cortex

Discovery sample activity										**Test sample activity**									
	region	**laterality**		**x**	**y**	**z**	**k**	**t**	**pFWE-corr**		**region**	**laterality**		**x**	**y**	**z**	**k**	**t**	**pFWE-corr**
WM										WM									
	dlPFC		left	−44	2	30	89	12.6	0.001		dlPFC		left	−46	4	30	47	8.12	0.003
	dlPFC		left	−50	10	30	54	10.6	0.003		dlPFC		left	−48	10	30	13	7.16	0.016
	dlPFC		left	−46	28	24	19	7.21	0.013		dlPFC		left	−44	30	20	10	6.19	0.019
	dlPFC		right	50	10	30	53	6.74	0.003		dlPFC		right	4	16	46	38	6.07	0.005
	dlPFC		right	46	4	28	14	6.56	0.016										
	dACC		left	−6	6	52	82	9.2	0.001		dACC		left	−2	8	52	90	8.17	0.001
	precuneus		right	32	−62	44	353	9.51	<0.001		precuneus		right	34	−52	50	36	7.27	0.005
											precuneus		right	10	−62	52	31	6.39	0.007
	precuneus		left	−26	−70	34	12	9.45	0.018		precuneus		left	−10	−64	52	17	5.67	0.013
	precuneus		left	−26	−64	44	337	9.35	<0.001		precuneus		left	−32	−56	50	88	8.87	0.001
ER										ER									
	dlPFC		left	−44	2	30	99	12	0.002		dlPFC		left	−40	2	28	58	9.73	0.003
	dlPFC		left	−48	10	30	54	10.5	0.007		dlPFC		left	−48	10	30	13	8.78	0.017
	dlPFC		left	−46	28	24	31	8.62	0.012		dlPFC		left	−44	30	20	27	8.57	0.009
	dlPFC		right	44	10	30	88	6.64	0.003		dlPFC		right	46	10	30	31	6.97	0.008
	dlPFC		right	42	2	28	16	6.16	0.021		dlPFC		right	48	8	38	59	6.37	0.003
	dACC		left	−6	6	52	79	8.18	0.004		dACC		left	−4	16	46	117	10.5	<0.001
											dACC		right	4	16	46	67	8.17	0.002
	precuneus		left	−32	−62	44	397	10.9	<0.001		precuneus		left	−32	−62	48	10	8.04	0.019
	precuneus		left	−26	−70	34	16	10.3	0.021		precuneus		left	−28	−62	50	115	11.7	0.001
											precuneus		left	−32	−62	48	11	11	0.019

Discovery sample activity										**Test sample activity**									
	region	**laterality**		**x**	**y**	**z**	**k**	**t**	**pFWE-corr**		**region**	**laterality**		**x**	**y**	**z**	**k**	**t**	**pFWE-corr**
											precuneus		left	−10	−64	52	56	7.12	0.003
	precuneus		right	12	−70	54	383	10.3	<0.001		precuneus		right	28	−60	44	74	8.81	0.002
											precuneus		right	8	−64	50	82	7.44	0.001
											caudate		left	−12	10	0	18	6.1	0.013
Discovery sample FC										**Test sample FC**									
	seed	**target**	**laterality**	**x**	**y**	**z**	**k**	**t**	**pFWE-corr**		**seed**	**target**	**laterality**	**x**	**y**	**z**	**k**	**t**	**pFWE-corr**
WM										WM									
	dlPFC	vACC	right	4	30	24	11	4.91	0.017		dlPFC	n/a							
	precuneus	dlPFC	left	−44	12	32	12	5.04	0.017		precuneus	n/a							
	dACC	n/a									dacc	n/a							
ER										ER									
	dlPFC	precuneus	right	12	−60	60	120	6.36	<0.001		dlPFC	precuneus	right	14	−52	50	74	5.81	0.001
		precuneus	right	8	−54	62	17	5.8	0.013			precuneus	right	24	−60	48	32	5.38	0.005
												precuneus	left	−8	−58	54	51	5.06	0.002
		dACC	right	6	24	28	28	4.96	0.007			dACC	right	4	20	40	42	5.58	0.003
												dACC	left	−2	18	40	62	5.37	0.001
												dACC	right	8	26	26	15	5.16	0.012
	precuneus										precuneus								
		dACC	left	−6	8	52	21	6.04	0.01			dACC	left	−6	20	46	19	5.11	0.008
		dlPFC	left	−48	16	26	62	7.12	0.002										
		dlPFC	left	−42	16	34	98	6.59	0.001										
		dlPFC	right	46	18	26	13	4.97	0.016										
	dacc	n/a									dacc	n/a							

Table 3:

A. Working memory activity and functional connectivity related to Hamilton Depression scale after variable selection with elastic net (steps 4 and 5 in analytic plan). **Discovery Sample;** B. Working memory related to Hamilton Depression scale **Test Sample.** Abbreviations: Confidence Interval (CI), dorsal anterior cingulate cortex (dACC), dorsolateral prefrontal cortex (dlPFC), False Discovery Rate (FDR) for each model. FDR across models within samples.

Parameter		B	Hypothesis Test					Exp(B)	95% CI for Exp(B)	
			Wald Chi-Square	df	Sig.	FDR	FDR across models		Lower	Upper
dlPFC (BA 9) *	left	0.59	23.49	1.00	0.000	0.000	0.000	1.80	1.42	2.28
precuneus *	right	0.36	8.25	1.00	0.004	0.004	0.008	1.43	1.12	1.82
dlPFC-dACC *	right	0.56	32.09	1.00	0.000	0.000	0.000	1.75	1.44	2.13
A. **Discovery Sample**										
Parameter		**B**	**Hypothesis Test**					**Exp(B)**	**95% CI for Exp(B)**	
			Wald Chi-Square	**df**	**Sig.**	**FDR**	**FDR across models**		**Lower**	**Upper**
dlPFC (BA 9) *	left	1.06	83.44	1.00	0.000	0.000	0.000	2.90	2.31	3.64
precuneus *	right	0.63	39.48	1.00	0.000	0.000	0.000	1.88	1.54	2.29
B. **Test Sample**										

* Benjamini-Hochberg FDR corrected adjusted pvalue <.05. Exp(B) = odds ratio or a 1 unit change in predictor variable is an Exp(B) increase in the dependent variable (depression score).

Table 4:

A. Emotional Regulation activity and functional connectivity related to Hamilton Depression scale after variable selection with elastic net (steps 4 and 5 in analytic plan). **Discovery Sample;** B. Emotional Regulation related to Hamilton Depression scale **Test Sample.** Abbreviations: Confidence Interval (CI), dorsal anterior cingulate cortex (dACC), dorsolateral prefrontal cortex (dlPFC), False Discovery Rate (FDR) for each model. FDR across models within samples.

Parameter		**B**	**Hypothesis Test**					**Exp(B)**	**95% Cl for Exp(B)**	
			Wald Chi-Square	**df**	**Sig.**	**FDR**	**FDR across models**		**Lower**	**Upper**
dlPFC (BA 9) *	left	1.45	15.89	1.00	0.000	0.000	0.000	4.27	2.09	8.72
dlPFC (BA 9)	left	−0.64	4.09	1.00	0.043	0.050	0.048	0.53	0.29	0.98
precuneus	right	0.40	3.00	1.00	0.083	0.083	0.083	1.49	0.95	2.35
dACC	left	0.68	4.34	1.00	0.037	0.052	0.046	1.97	1.04	3.74
precuneus-dACC *	left	0.49	4.96	1.00	0.026	0.046	0.037	1.64	1.06	2.53
precuneus-dlPFC *	right	0.51	10.03	1.00	0.002	0.007	0.005	1.67	1.22	2.29
dlPFC-dACC *	right	0.40	6.25	1.00	0.012	0.028	0.020	1.49	1.09	2.04
A. **Discovery Sample**										
Parameter		**B**	**Hypothesis Test**					**Exp(B)**	**95% CI for Exp(B)**	
			WaldChi-Square	**df**	**Sig.**	**FDR**	**FDR across models**		**Lower**	**Upper**
dlPFC (BA 9) *	left	0.98	37.06	1.00	0.000	0.000	0.000	2.65	1.94	3.63
precuneus-dACC *	left	2.42	118.37	1.00	0.000	0.000	0.000	11.22	7.26	17.34
dlPFC-dACC *	right	0.96	33.94	1.00	0.000	0.000	0.000	2.61	1.89	3.60
B. **Test Sample**										

* Benjamini-Hochberg FDR corrected adjusted pvalue <.05. Exp(B) = odds ratio or a 1 unit change in predictor variable is an Exp(B) increase in the dependent variable (depression score).

Table 5:

A. Harmonized sample working memory activity and functional connectivity related to Hamilton Depression scale up to 12 months post-scan (step 6 in analytic plan); B. Harmonized sample emotional regulation with working memory activity and functional connectivity related to Hamilton Depression scale up to 12 months post-scan (step 6 in analytic plan). Abbreviations: Confidence Interval (CI), dorsal anterior cingulate cortex (dACC), dorsolateral prefrontal cortex (dlPFC), False Discovery Rate (FDR) for each model. FDR across models within samples.

Parameter		**B**	**Hypothesis Test**					**Exp(B)**	**95% CI for Exp(B)**	
			WaldChi-Square	**df**	**Sig.**	**FDR**	**FDR across models**		**Lower**	**Upper**
days between scan and follow up		0.06	0.38	1.00	0.537	0.537	0.537	1.06	0.88	1.28
dlPFC (BA 9) *	left	1.03	71.50	1.00	0.000	0.000	0.000	2.81	2.21	3.56
precuneus *	right	0.40	13.83	1.00	0.000	0.000	0.000	1.49	1.21	1.85
A. **Harmonized Sample**										
Parameter		**B**	**Hypothesis Test**					**Exp(B)**	**95% CI for Exp(B)**	
			Wald Chi-Square	**df**	**Sig.**	**FDR**	**FDR across tasks**		**Lower**	**Upper**
days between scan and follow up		0.14	1.35	1.00	0.245	0.245	0.285	1.15	0.91	1.46
dlPFC (BA 9)	left	1.27	52.54	1.00	0.000	0.000	0.000	3.55	2.52	5.00
precuneus-dACC *	left	1.83	42.97	1.00	0.000	0.000	0.000	6.26	3.62	10.83
dlPFC-dACC *	right	1.29	32.61	1.00	0.000	0.000	0.000	3.65	2.34	5.68
B. **Harmonized Sample**										

* Benjamini-Hochberg FDR corrected adjusted pvalue <.05. Exp(B) = odds ratio or a 1 unit change in predictor variable is an Exp(B) increase in the dependent variable (depression score).