Family History of Depression is Associated with Alterations in Task-Dependent Connectivity between the Cerebellum and Ventromedial Prefrontal Cortex

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Abstract A family history of major depressive disorder (MDD) increases the likelihood of a future depressive episode, which itself poses a significant risk for disruptions in reward processing and social cognition. However, it is unclear whether a family history of MDD is associated with alterations in the neural circuitry underlying reward processing and social cognition. To address this gap, we subdivided 279 participants from the Human Connectome Project into three groups: 71 with a lifetime history of MDD (Dep), 103 with a family history of MDD (Fam), and 105 healthy controls (HC). We found that Fam (relative to HCs) were associated with increased sadness scores, and Dep (relative to both Fam and HC) were associated with increased sadness and MDD symptoms. We then evaluated task-based fMRI data on a social cognition and reward processing task and found a region of the ventromedial prefrontal cortex (vmPFC) that responded to both tasks, independent of group. To investigate whether the vmPFC shows alterations in functional connectivity between groups, we conducted psychophysiological interaction (PPI) analyses using the vmPFC as a seed region. These analyses revealed that Fam groups had increased vmPFC functional connectivity within the nucleus accumbens, left dorsolateral PFC and subregions of the cerebellum relative to HCs during the social cognition task. These findings suggest that aberrant neural mechanisms among those with a familial risk of MDD may underlie vulnerability to altered social cognition.

Introduction

Major Depressive Disorder (MDD) substantially interferes with the ability to carry out a normal life. As a leading contributor to global disability (World Health Organization, 2017; Ferrari et al., 2013), MDD carries profoundly disruptive symptoms that range from hopelessness (Abramson et al., 1989; Iacoviello et al., 2010), diminished motivation (Sherdell et al., 2012; Treadway et al., 2012) as a part of anhedonia (American Psychiatric Association, 2003; Pizzagalli, 2014), and is a prominent predictor of suicidality (Klonsky et al., 2016; Nock et al., 2009). Symptom recurrence is likely (Kovacs et al., 2016; Soloman et al., 2000), and each subsequent episode increases the chance that more will follow (Colman et al., 2011; Hoertel et al., 2017). Importantly, the probability that an individual will experience MDD during their lifetime intensifies for those with a family history of depression (Klein et al., 2005; Klein et al., 2013; Monroe et al., 2014; Zimmerman et al., 2008). Indeed, those with depressed first-degree relatives are nearly three times as likely to develop the disorder later in life (Sullivan et al., 2000). Upon the onset of MDD, the systems that support social cognition are also affected (Cusi et al., 2011; Derntl et al., 2011), which limits the capacity to maintain supportive connections with others and negatively impacts recovery (George et al., 1989; Santini et al., 2015). Understanding the abnormalities among the neural mechanisms underlying social cognition and reward sensitivity in MDD, and how they are vulnerable in those with a familial risk of MDD, stands to elucidate the relationship between early pathophysiology in the brain and subsequently altered cognition.

A wealth of research suggests that many of the symptoms associated with MDD involve abnormalities in specific neural circuits. For example, studies have found grey matter volume

reductions in frontotemporal areas (Cai et al., 2015; Serra-Balsco et al., 2013), the hippocampus (Arnone et al., 2013; Zhao et al., 2014), the orbitofrontal cortex (OFC; Bremner et al., 2002; Lacerda et al., 2004), the ventromedial prefrontal cortex (vmPFC; Wise et al., 2017), the dorsomedial prefrontal cortex (dmPFC), the anterior cingulate cortex (ACC), and the bilateral insula (Caetano et al., 2006; Salvadore et al., 2011). Recent reports also indicate a putative role for cerebellar grey matter volume decrease in depression (Wise et al., 2017). Indeed, abnormal structural circuitry in the cerebellum appears to underlie many common mental disorders (Romer et al., 2018). Likewise, white matter fractional anisotropy investigations also show disruptions across the lifespan among individuals with depression (Alexopoulous et al., 2008; Bae et al., 2006; Cruwys et al., 2014; Cullen et al., 2010; Steingard et al., 2002; Taylor et al., 2004; Yang et al., 2007). In conjunction with structural changes, MDD appears to produce functional aberrations in systems associated with reward processing. Evidence of differences in activation and connectivity in healthy individuals relative to those with MDD typically implicate the OFC (Cheng et al., 2018; Ng et al., 2019), the ventral striatum (VS; Furman et al., 2011; Kumar et al., 2018; Robinson et al., 2012), and the vmPFC (Koenigs et al., 2008; Myers-Schulz & Koenigs, 2012). Together, this work suggests that we may be able to understand some of the canonical symptoms seen in MDD symptomatology by taking a closer look at the neural correlates that underlie them.

Tied to the functional and structural impairments seen among reward processing systems (e.g., the striatum), a hallmark symptom of MDD involves the marked loss in the ability to experience pleasure (Cooper et al., 2018). Individuals with MDD often endure significant decreases in motivation (Hershenberg et al., 2015), diminishes in emotional responses to things that are pleasant (Alloy et al., 2016), and no longer pursue the interests they once found enjoyable (Fried & Nesse,

2014). Moreover, research implicates that social rewards share the neural circuitry represented by non-social rewards (Bhanji and Delgado, 2014; Fareri & Delgado, 2014). Thus, abnormalities in reward processing often overlap with social cognitive deficits, as reward system activation is critical for facilitating positive social exchanges (Carta et al., 2019; Smith & Delgado, 2017; Wang et al., 2016). Deficits in social cognition persist throughout recovery from MDD (Inoue et al., 2004), and are associated with later relapse (Inoue et al., 2006; Yamada et al., 2015). Individuals with a family history of depression also appear to be at risk for similar degrees of deviation in reward and social processing early on (Monk et al., 2008; Weinberg et al., 2013). For example, individuals with a familial risk of depression show abnormal responses to reward and punishment (McCabe et al., 2012), have reduced activity in the VS and ACC in response to social reward during adolescence (Olino et al., 2015), and decreased VS and anterior insula activity in response to non-social rewards during childhood (Luking et al., 2016). Furthermore, those with a familial history of MDD begin to show alterations in theory of mind processing - the ability to infer the mental states of others (Harkness et al., 2011).

However, despite the work underscoring the relationship between reward, social cognition, and depression, it remains unclear whether individuals with a familial history of MDD demonstrate neural alterations associated with processing social stimuli in the absence of reward. Investigating how the neural and behavioral alterations observed in MDD emerge in association with a family history is key to understanding the mechanisms that drive these changes. Moreover, evaluating cases with a predisposition to such alterations may inform current treatment practices that can help provide early intervention upon the identification of at-risk populations. Thus, in the present study, we investigate whether a family history of depression, in the absence of a personal diagnosis, is

associated with altered social cognition and reward processing in the brain. Our analyses focused on three main hypotheses (pre-registration found at http://aspredicted.org/blind.php?x=8qw2h3). First, we expected to see increased uncertainty during theory of mind processing, as well as increased depressive symptoms, reports of sadness, alcohol, and tobacco use among individuals with a personal history of MDD, relative to those with a family history of MDD or healthy controls. Second, we predicted that MDD groups would show blunted temporoparietal junction (TPJ) response and increased vermis and posterior cerebellar activity during the theory of mind task, and decreased striatal activation in response to reward during the gambling task. Our third hypothesis expected MDD groups to show decreased connectivity between the cerebellum's bilateral lobule VIIb and the vmPFC during the social task. Among all of these hypotheses, we anticipated a dose-dependent type of effect across all three groups, where MDD groups would show the highest magnitude of difference relative to familial risk or healthy control groups, with familial risk groups beginning to mirror any effects seen in MDD.

Materials and Methods

Participants. The sample included 279 participants (males, 120; females, 159; ages, 22-36; mean ± SD, 28.45 ± 3.75 years) selected from the Human Connectome Project (HCP) dataset, a large collection of primarily healthy young adults (N=1206) from the Q7 HCP release (MGH-USC Human Connectome Project; RRID:SCR_003490; Van Essen et al., 2013). The study protocol was performed in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Participants provided written informed consent, and procedures were approved by the ethics committee in accordance with guidelines of WU-Minn HCP. We subdivided participants into three groups. The depression (Dep) group (N=71) was selected on the basis of a lifetime history of a DSM-IV Major Depressive Episode diagnosis (SSAGA_Depressive_Ep=5; N=71).

The family history (Fam) group (N=103) was selected if they had not received a DSM-IV Major Depressive Episode diagnosis in their lifetime (SSAGA_Depressive_Ep=1), but either their mother (FamHist_Moth_Dep=1) or father (FamHist_Fath_Dep=1) had. Healthy controls (HC; N=105) consisted of participants who had not received a DSM-IV Major Depressive Episode diagnosis in their lifetime (SSAGA_Depressive_Ep=1), and had no family history of psychiatric or neurologic disorders (FamHist_Moth_None=1 and FamHist_Fath_None=1). The number of HCs that qualified for these conditions was large (N=573); to facilitate comparison, we randomly selected HC participants to match our largest experimental group (N=105).

Participants were considered outliers and excluded if they demonstrated poor neuroimaging data quality (e.g., excessive head motion). Outliers were identified with a boxplot threshold (Smith et al., 2014). Additionally, participants who met DSM-4 criteria for alcohol abuse (SSAGA_Alc_D4_Ab_Dx) were excluded from the current study.

Task Paradigms

All 279 participants in the current study performed 7 tasks in the scanner across two sessions, with two runs of each task. Here, we analyze data from only 2 tasks: social cognition and reward processing. The descriptions of the two tasks of interest here are adaptations of the details in Barch et al. (2013) and are provided through the Human Connectome Project Data Dictionary available online: https://wiki.humanconnectome.org/display/PublicData/HCP+Data+Dictionary+Public-+Updated+for+the+1200+Subject+Release.

Social cognition. During the scans, participants engaged with a cognitive task previously implicated as a robust and reliable measurement of social theory of mind processing (Castelli et al., 2000; Castelli et al., 2002; Wheatley et al., 2007; White et al., 2011). The task consists of brief

animations of geometric shapes (e.g., squares, circles, triangles) moving dynamically across the screen. The movement of the shapes was designed to either drift randomly, or in a way that is suggestive of a social interaction. In the social interaction categories, the shapes are presented to appear aware of each other, suggestive of mentalizing capabilities, such as taking into account the thoughts and feelings of other shapes (Barch et al., 2013). Participants were instructed to indicate whether they interpreted a social interaction, no social interaction, or if they were unsure of social interaction among the geometric shapes. The task was presented in two runs of 10 blocks with 5 videos (20s) and 5 fixation blocks (15s). Blocks were counterbalanced across runs, with one run consisting of 2 "social" videos and 3 "random" videos (i.e., mostly random), and the other run consisting of 3 "social" videos and 2 "random" videos (i.e., mostly social), interleaved with fixation blocks.

Reward Processing. To assess group differences in neural activity underlying reward consumption, participants also engaged with an adaptation of a previously described incentive processing task (Delgado et al., 2000). This task was selected to test hypotheses surrounding altered reward activity in the striatum, as it demonstrates robust and reliable activity in this region and other reward-related regions across multiple participants (Forbes, 2009; May et al., 2004). During the scan, participants were prompted (1.5s) to guess whether the value of a blank card (i.e., a "mystery" card) was higher or lower than 5 (from a range of 1-9) by selecting a button on an in-scanner handheld response box. Participants received feedback on the outcome of their choice (1s), where a green $1 indicated that the participant would receive this amount as a reward, and a red -$0.50 indicated a punishment of that amount. Trials (3.5s each) were arranged in predetermined blocks of primarily reward or primarily loss; a majority reward block contained 8 trials with 6 of

them exclusively reward, pseudo-randomly interleaved with 2 loss trials, 2 neutral trials, or one of either (Barch et al., 2013).

Image Acquisition

HCP sample fMRI data acquisition are described in extensive detail elsewhere (Glasser et al., 2013; Smith et al., 2013; Uğurbil et al., 2013; Van Essen et al., 2013). All 279 participants in the current study underwent T1 and T2-weighted structural scans, resting-state and task-based fMRI scans, and diffusion-weighted MRI scans, all via a 3T Siemens scanner with a standard Siemens 32 channel RF head coil. Identical multi-band EPI sequence parameters leveraged high spatial resolution at 2mm isotropic using the following parameters: repetition time (TR) = 720 ms; echo time (TE) = 33.1 ms, 72 slices, 2mm isotropic voxels, using a multi-band acceleration factor of 8 (Feinberg et al., 2010; Moeller et al., 2010; Setsompop et al., 2012; Xu et al., 2012). The current investigation used minimally preprocessed BOLD fMRI data to increase ease of use and mitigate the possibility of complex issues relating to imaging data quality (Glasser et al., 2013) such as CSF or white matter noise, or nonlinear image distortion. As mentioned previously, tasks were performed twice, with one run in a left-to-right direction, and then reversed in the second run.

fMRI Preprocessing

As mentioned above, the imaging data provided by the HCP database received minimal preprocessing; the general preprocessing steps are briefly summarized here and presented in full detail in the previous reports (e.g., Glasser et al., 2013, Van Essen et al., 2012) primarily using tools built by FSL (Jenkinson et al., 2002; Jenkinson et al., 2012) and FreeSurfer (Fischl, 2012). To produce a structural volume space per subject without distortion, Glasser and colleagues report

using fMRIVolume to remove spatial distortion, account for subject motion through volume realignment, reduce bias field, normalize the 4D image to a common average, and mask data with the outputted brain mask. T1- and T2-weighted images were aligned with a 12 degree of freedom (affine) registration to the Montreal Neurological Institute (MNI) space templates, first using an initial FLIRT (linear) followed by a FNIRT (non-linear) registration. We added an additional layer of preprocessing to our social cognition and reward task fMRI data. First, we smoothed the data with a spatial smoothing of 6mm and the entire 4D dataset received grand-mean intensity normalization using a single multiplicative factor. Next, we identified and removed artifacts sourced from excess head-motion using the ICA-AROMA Software Package.

fMRI Analysis

We analyzed task-based fMRI data using FEAT (FMRI Expert Analysis Tool) Version 6.00, part of FSL (FMRIB's Software Library; Jenkinson et al., 2012). Specifically, we used FILM (FMRIB's Improved Linear Model) with local autocorrelation correction (Woolrich et al., 2001) to assess task-evoked changes in neural responses to social and reward stimuli.

To assess neural responses to social and reward-related stimuli, we employed two main models. Both models employed a general linear model (GLM) approach. Each first level GLM included two regressors to account for the block structure in a task. For the gambling task, we used two regressors: one for reward, and one for loss. The reward regressor was modeled from the onset of the first trial of the block which consisted of mostly reward until the offset of that block; similarly, the punishment regressor was elicited the same way, but drawn from the mostly-loss blocks. We also had two regressors for the social task: one for mental trials, and one for random trials. The mental regressor was modeled from the onset of the first block of the run that consisted of mostly

mental videos until the offset of that run; the random regressor was similarly derived from the run that consisted of mostly random trials. Each of our models were convolved using the canonical haemodynamic response function.

To investigate task-evoked changes in brain connectivity, we utilized a psychophysiological interaction (PPI) analysis (Friston et al., 1997). Notably, PPI has been shown to produce consistent and specific patterns of task-dependent connectivity in recent meta-analytic work (Smith et al., 2016; Smith & Delgado 2017). Our PPI models focused on cerebellar coupling with vmPFC and were later expanded in an exploratory whole brain analysis, maintaining the vmPFC as the seed region. For this analysis, we thresholded and corrected for multiple comparisons within a priori regions of interest (ROI; http://aspredicted.org/blind.php?x=8qw2h3) at the voxel level. ROIs were identified via a Cerebellar Atlas in MNI152 space after normalization with FNIRT and the Harvard-Oxford cortical and subcortical atlases in FSL. In addition to the same regressors used in the activation models, our PPI models included regressors to represent the activation time course in connectivity between the vmPFC seed region and cerebellar target regions. Similar to our analysis of activation, we evaluated two distinct PPI models for each task: the social cognition and reward processing tasks.

To combine data across runs for our second-level analysis, we used a fixed effects model, with random effects variance forced to zero in FLAME (Beckmann et al., 2003; Woolrich et al., 2004; Woolrich, 2008). Next, we combined data across subjects using FLAME (FMRIB's Local Analysis of Mixed Effects) stage 1 (Beckmann et al., 2003; Woolrich et al., 2004; Woolrich, 2008). To detect group differences in neural activity for the social cognition and reward processing tasks, and to control for other factors influence our results, we used a general linear model consisting of 11 regressors. The 11 regressors contained data describing participant head movement during the

task, gender, depressive symptoms, sadness scores, impulsivity, alcohol and tobacco use. Gaussianized z-statistic images were thresholded with voxel-level GRF-theory-based maximum height thresholding with a corrected significance threshold of p=0.05 (Worsley, 2001). We controlled for family structure in the data (Winkler et al., 2015) using PALM (Winkler et al., 2014) to evaluate our models and control for multiple comparisons.

Results

Behavioral and Clinical Analyses. Our analyses began by testing whether a family history of depression increased depression symptoms and sadness experienced across one's lifetime. To compare depression symptoms, we evaluated the average number of lifetime depressive symptoms reported by each participant that met DSM-IV criteria. We found that individuals with a family history reported more lifetime depressive symptoms across their lives compared to healthy controls (t(206)=2.54, p=0.011). Individuals in the depression group had higher depressive symptom rates than both family history (t(172)= 19.22, p<0.01) and healthy control (t(174)=27.00, p<0.01; see Figure 1A) groups. Similarly, we used unadjusted self-report scale scores as measured by the NIH Toolbox Sadness Survey to compare reports of sadness across each group. We found that unlike the depressive symptoms, sadness scores in participants with a family history of depression did not differ significantly from healthy controls (t(206)=1.88, p=0.06). However, as expected, the levels of sadness as reported by the depression group surpassed both family history (t(172)=4.39, p<0.01) and healthy control groups (t(174)=6.09, p<0.01, See Figure 1b). Additionally, we tested for differences in alcohol and tobacco use (in the past 7 days) between groups, as previous work has found a relationship between tobacco use (Edwards et al., 2011) or occasional bouts of heavy

drinking (Manninen et al., 2006) and depression. However, we did not find significant differences in either alcohol or tobacco use across groups (see Table 1).

We hypothesized that depression groups will be more unsure about the social nature of the stimuli relative to family history or healthy control groups. To test this hypothesis, we compared the selections each group made while engaging with the theory of mind task in the scanner. Contrary to our expectations, we found that the depression group had a higher percentage of 'social' selections relative to family history ($t(172)=5.81$ $p<0.01$) and healthy control ($t(174)=5.66$, $p<0.01$) groups. The depression group also demonstrated lower percentages of 'random' selections relative to family history ($t(172)=-3.89$ $p<0.01$) and healthy control ($t(174)=-3.87$, $p<0.01$) groups. Depression and family history ($t(172)=-1.81$ $p=0.07$), depression and healthy controls ($t(174)=-0.57$, $p=0.57$); family history and healthy controls ($t(206)=1.41$, $p=0.16$) did not differ significantly with respect to percentage of 'unsure' selections throughout the task (see Figure 1c).

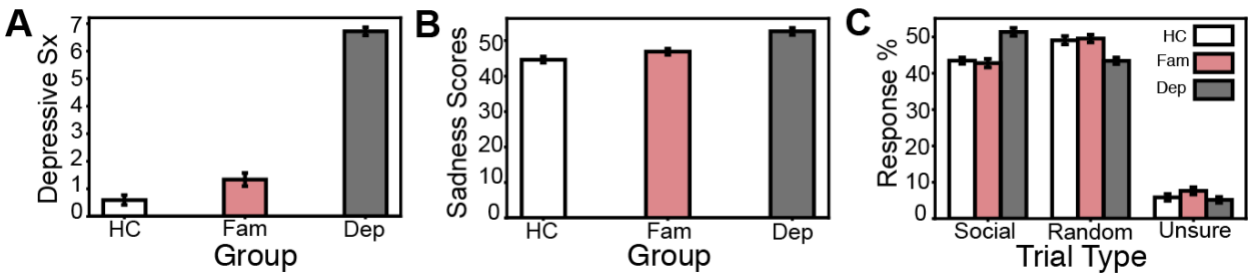

Figure 1: Depression symptoms and unadjusted sadness scores across depression, family history, and healthy control groups. ***A***, Depression (Dep) groups show higher average depression symptoms compared to both individuals with a family history of depression (Fam; $t(172)= 19.22$, $p<0.01$) and healthy controls (HCs; $t(174)=27.00$, $p<0.01$). Individuals in the Fam group show higher depression symptoms compared to HCs ($t(206)=2.54$, $p=0.011$). ***B***, Unadjusted sadness scores are significantly higher in Dep when comparing to both Fam ($t(172)=4.39$, $p<0.01$) and HC groups ($t(174)=6.11$, $p<0.01$), but did not reach our significance threshold between Fam and HCs ($t(206)=1.88$, $p=0.06$). ***C***, Average social, random, and unsure percent responses to a Theory of Mind (ToM) social cognition task presented to participants during the fMRI scanning paradigm. Dep showed a higher percentage of 'social' selections relative to family history ($t(172)=5.81$ $p<0.01$) and healthy control ($t(174)=5.66$, $p<0.01$) groups. Dep also demonstrated lower percentages of 'random' selections relative to Fam ($t(172)=-3.89$ $p<0.01$) and HCs ($t(174)=-3.87$, $p<0.01$). Dep and Fam ($t(172)=-1.81$ $p=0.07$), Dep and HCs ($t(174)=-0.57$, $p=0.57$); Fam and HCs ($t(206)=1.41$, $p=0.16$) did not differ significantly with respect to percentage of 'unsure' selections throughout the task.

Group	Participants (N)	Gender	Alcohol Use	Tobacco Use
Depression (Dep)	71	61% F; 40% M	4.661	5.450
Family history (Fam)	103	62% F; 38% M	4.165	6.533
Healthy controls (HC)	105	50% F; 50% M	4.295	5.123

Table 1: Percentage of male and female participants, as well as average tobacco and alcohol used in the past 7 days across each group. Groups did not differ significantly in their use of alcohol over the past 7 days. Alcohol use in Dep and Fam: ($t(172)=0.47$, $p=0.63$), Dep and HCs ($t(174)=0.34$, $p=0.73$), Fam and HCs ($t(206)=-0.15$, $p=0.88$). Similarly, there were no differences in tobacco use between Dep and Fam ($t(172)= -0.36$, $p=0.71$), Dep and HCs ($t(174)= 0.12$, $p=0.90$), and Fam and HCs ($t(206)=0.51$, $p=0.61$).

ROI Analyses

Next, we evaluated whether the social cognition and reward processing tasks activate canonical mentalizing and reward processing regions respectively, and if activity overlaps. We found that independent of group, the social cognition task activated the temporoparietal junction on the mental > random trial contrast, and the reward processing task activated the nucleus accumbens on the reward > punishment trial contrast. A subsequent conjunction analysis revealed that a region of the ventromedial prefrontal cortex (vmPFC) responded to both tasks, independent of groups (Figure 2). We then used this region of the vmPFC as a seed for psychophysiological interaction (PPI) analyses to evaluate vmPFC connectivity patterns with the cerebellum and later, across the entire brain.

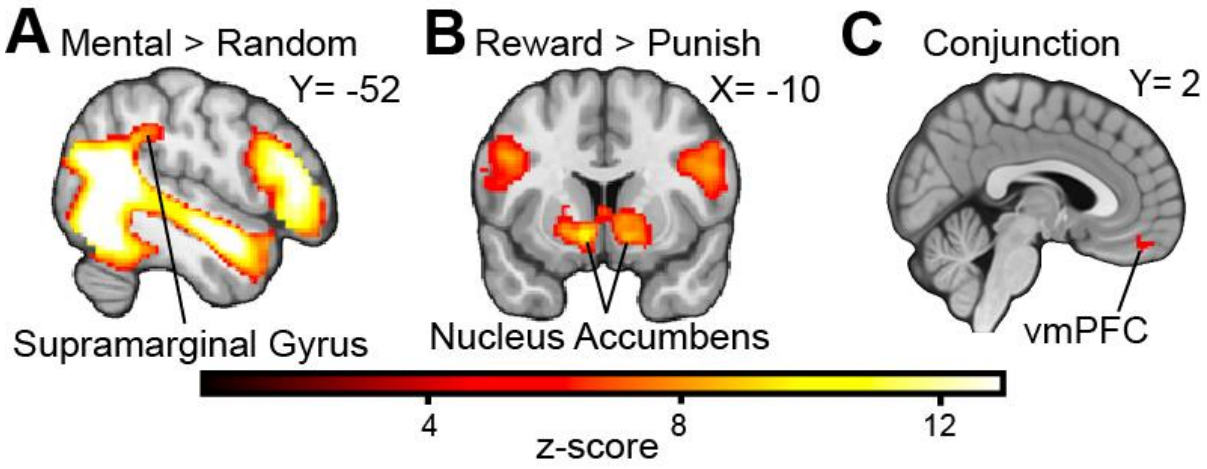

Figure 2: Activation and Conjunction Analyses. ***A***, Independent of group, the social cognition task evoked activity in the temporoparietal junction specific to Mental > Random trials contrasts. ***B***, Similarly, the reward processing task evoked striatal activation on the Reward > Punishment trial contrasts. ***C***, Both tasks also demonstrate shared activation in a region of the ventromedial prefrontal cortex (vmPFC). Gaussianized z-statistic images were thresholded with voxel-level GRF-theory-based maximum height thresholding with a corrected significance threshold of p=0.05.

We then evaluated for the presence of dose-dependent responsivity among the groups during a social cognition task. We predicted that during this task, Dep would demonstrate blunted TPJ activation, but increased cerebellar activity, particularly in the vermis and posterior hemispheres relative to healthy control and family history groups. Our dose-dependency hypotheses also anticipated that while depression groups would show the largest responses (either by way of increase or decrease), the family history groups would trend towards the pattern exhibited by the depression group, with blunted TPJ activation and increased cerebellar activity relative to healthy controls. Additionally, we expected to see that depression groups would have blunted striatal activation in response to the reward processing task, relative to healthy control and family history groups, while family history groups also show blunted striatal activation relative to healthy controls. Despite these hypotheses, we found no differences in TPJ or cerebellar activation within the social task, nor striatal activation differences during the reward processing task across the groups.

Our pre-registered hypotheses also included connectivity differences, and we expected to see decreased vmPFC-cerebellar (specifically with respect to the bilateral lobule VIIb) connectivity during the social cognition task for depression groups relative to family history and healthy control groups. As with our activation hypotheses, we expected that family history groups would also show decreased connectivity between the vmPFC and cerebellar subregions, albeit relative to healthy controls. Our results do not show any differences in vmPFC-cerebellar functional connectivity between depression and family history groups, nor when comparing depression and healthy controls. Nevertheless, we find increased in vmPFC-cerebellar functional connectivity in family history groups relative to healthy controls. Specifically, relative to healthy controls, the family history group shows increases in connectivity between the vmPFC and the left crus I of the cerebellum during the mentalizing trials. Random trials, on the other hand, showed increased connectivity between the vmPFC and VIIb region of the cerebellum, with the family history group again showing a greater response than the healthy controls in particular (see Figure 3).

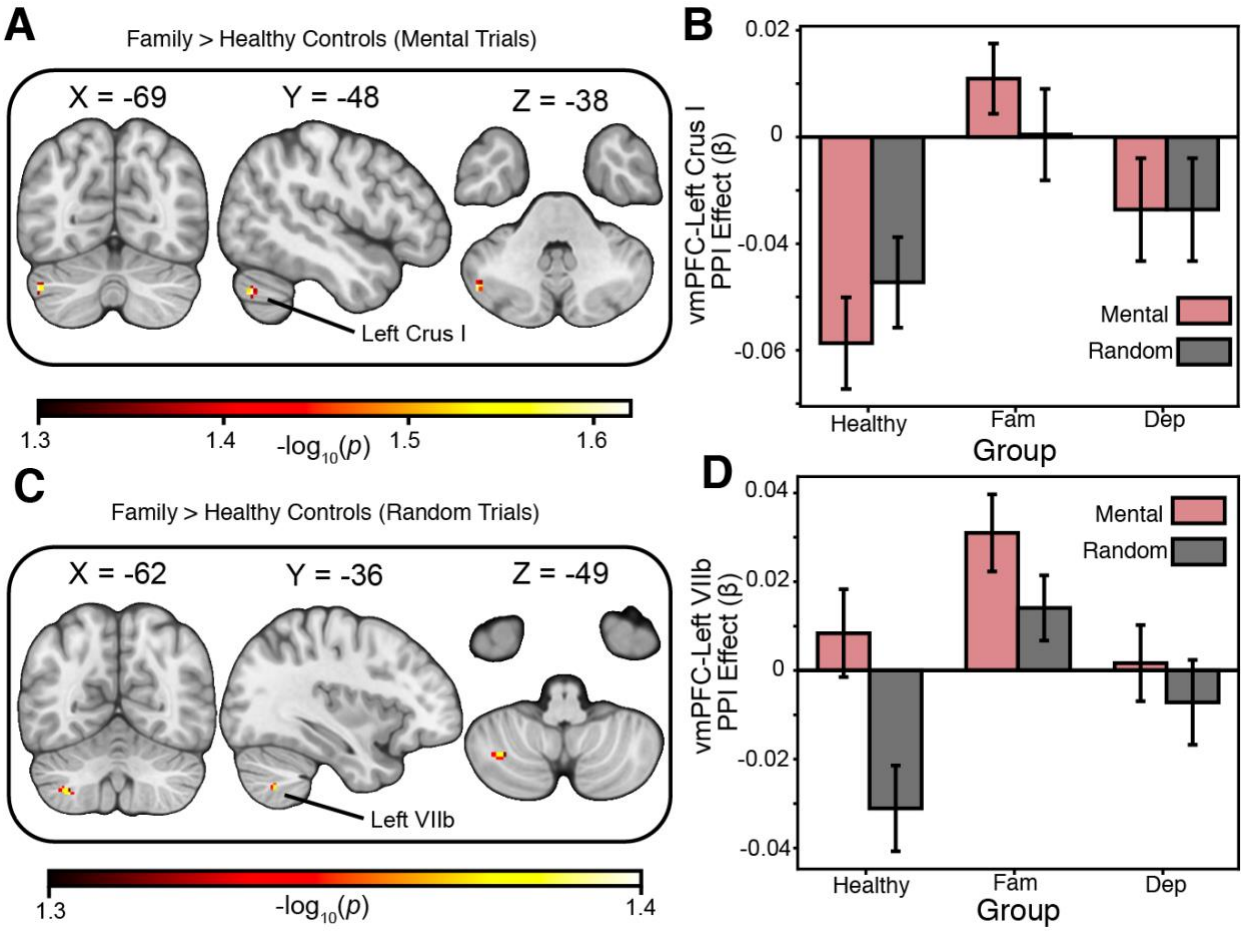

Figure 3: Psychophysiological (PPI) analysis using vmPFC as the seed region. ***A***, Relative to healthy controls, the family history group showed increased in task-based functional connectivity between the vmPFC and the left crus I of the cerebellum during the "Mentalizing" trials. Areas of activation passed an a priori small volume correction (cerebellum) using threshold-free-cluster enhancement (TFCE) and permutation-based testing using PALM. ***B***, Interrogation of the left Crus I region of the cerebellum revealed increased activation relative to the decrease in activation seen in healthy controls during the mental trials. ***C***, increased connectivity between the vmPFC and VIIb region of the cerebellum was selective for the random stimuli in the social task, with the family history group showing a greater response than the healthy controls. Areas of activation passed an a priori small volume correction (cerebellum) using threshold-free-cluster enhancement (TFCE) and permutation-based testing using PALM. ***D***, Interrogation of the left VIIb region of the cerebellum showed family history groups had a larger increase in activation relative to healthy controls during the mental trials.

Exploratory Analyses

Finally, we expanded our search beyond the pre-registered hypotheses and a priori cerebellar target to include a whole-brain analysis of vmPFC connectivity. We again find functional connectivity differences only between family history groups and healthy controls during the social cognition

task. Specifically, individuals with a familial risk of depression, relative to healthy controls, demonstrated increased vmPFC-nucleus accumbens and vmPFC-dorsolateral PFC functional connectivity during the mentalizing trials (see Figure 4).

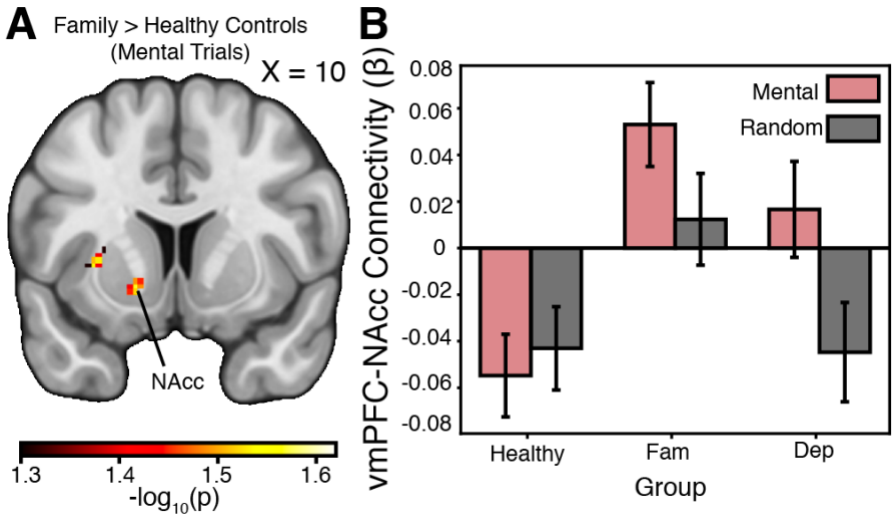

Figure 4: Exploratory whole-brain analysis. A, Relative to healthy controls, family history groups showed greater task-based functional connectivity between the vmPFC and the nucleus accumbens (NAcc) during the mental trials of the social cognition task. Areas of activation passed a whole brain correction using threshold-free-cluster enhancement (TFCE) and permutation-based testing. B, Interrogation of the NAcc revealed that increased activation in the family history groups, while the healthy control groups demonstrate a relative decrease in activation during the mental trials.

Discussion

A deeper understanding of the neural mechanisms underlying social cognition and reward processing can elucidate how these systems typically function, and the conditions under which they can become susceptible to change. Mapping task-based neural activity among those with a well-established risk factor for MDD allows us to probe at this susceptibility to change in reward and social systems. Moreover, capturing the state of the brain before MDD onset in an at-risk group is especially relevant to clinical efforts in treatment and intervention. Thus, the goal of the current study centered on evaluating task-based neural processing of social and reward systems in

those with a familial vulnerability to major depressive disorder, using data from the Human Connectome Project. In line with our expectations, we found that relative to healthy controls, individuals with a family history of MDD demonstrate increases in depressive symptoms, and MDD groups showed increased sadness scores and depressive symptoms relative to both family history and healthy control groups. Yet, we did not find significant neural differences between healthy controls and those with a personal history of MDD on either social or reward processing tasks as expected. Nevertheless, we confirmed our initial hypothesis that family history groups would show neural alterations relative to healthy controls during the social cognition task. Specifically, we found that relative to healthy controls, individuals with a family history of MDD demonstrated increased task-dependent functional connectivity between the ventromedial prefrontal cortex (vmPFC) and the nucleus accumbens, left dorsolateral PFC, and subregions of the cerebellum during a mentalizing task. Altogether, these results reveal that in addition to upticks in pre-clinical reports of depressive symptoms, individuals with a family history of depression may be at risk for neural abnormalities underlying theory of mind processes, with altered cerebellar-vmPFC functional connectivity contributing to this difference.

A host of recent studies have begun to reveal the functional role of the cerebellum in social, cognitive, and affective neuroscience (Van Overwalle et al., 2015; Van Overwalle et al., 2014). For example, the cerebellum has been linked to social reward (Carta et al., 2019), social preference (Badura et al., 2018), and emotional processing (Baumann & Mattingley, 2012). Of particular relevance to our current results, the cerebellum has been linked to mentalizing processes by way of connectivity with the cortex, including the temporoparietal junction (Van Overwalle et al., 2019) and dorsomedial prefrontal cortex (Van Overwalle et al., 2015). Cerebellar connectivity has also been tied to the default mode network (Buckner 2011), which participates in social inference

(Bucker & DiNicola, 2019). In light of this past work, the present study dovetails with the existing literature by providing additional evidence demonstrating involvement of cerebellar connectivity during mentalizing. Specifically, our findings implicating task-based vmPFC-cerebellar connectivity differences in a theory of mind task appears to fall in line with previous suggestions that the cerebellum is involved in social reasoning (Van Overwalle et al., 2019).

Unlike prior studies of the cerebellum, our work highlights a novel role for the region's involvement in the vulnerabilities inherited through a family history of depression. While investigations of autism (Becker & Stoodley, 2013), schizophrenia (Andreason & Pierson, 2008), and major depressive disorder (Liu et al., 2012) have shown alterations in the cerebellum related to social and affective processing, these data demarcate populations that have already developed a disorder. As such, relatively little is known about the neural signatures involved in a family history of depression as it relates to social cognition. Through the identification of altered task-based cerebellar functional connectivity with the vmPFC, we shed new light on possible mechanisms at play that may lead to the early stages of MDD. In addition to building a deeper understanding of the cerebellum's role in social cognition, this work lends itself to inform interventions geared towards mitigating later emergence of MDD. Indeed, considering the cerebellum's influence on social and cognitive development, the region has previously been suggested as a potential site for treatment (Wang et al., 2014). Moreover, altered functional connectivity between the cortex and cerebellum can reliably predict the presence of depression (Ma et al., 2013). The results of the present study indicate that consideration for the cerebellum as a therapeutic target may be promising early on, before the onset of MDD.

Although our study demonstrates that task-dependent connectivity with the cerebellum is altered in those with a family history of depression, we note that our findings are accompanied by some

limitations. For example, our results that vmPFC-cerebellar connectivity was enhanced in family history groups relative to healthy controls was not specific to the mental nor random conditions in the social task. We speculate that the lack of differences between the two conditions in the social task could be due to the nature of the task. Indeed, although the task used by the HCP is a robust probe of TPJ activation, it may not evoke similar levels of activation in other regions that process more subtle differences in how participants process and interpret a range of social interactions. Future work building on these findings would do well to involve measures of social cognition that characterize mental representations of others in a variety of ways. For instance, it may be particularly relevant to examine social interactions as seen in the virtual school paradigm (Jarcho et al., 2016), as this may better probe at how the cerebellum processes the mental states of characters in a more ecologically valid setting.

In addition to limitations with the social task, we also note that our study may not be able to speak directly to the mechanisms underlying risk for developing MDD, given the cross-sectional nature of the Human Connectome Project. Although our original hypothesis—that aberrant patterns of connectivity would deviate further from healthy controls when examining people with a personal history of depression—was not supported by our findings, we note that this is an area where longitudinal data would be necessary for understanding whether and how altered connectivity is associated with the development of MDD. To address this question, future research could leverage other open datasets that include longitudinal assessments of cerebellar connectivity, such as the Adolescent Brain Cognitive Development study (ABCD; Casey et al., 2018). Thus, in the absence of longitudinal data, it is unclear whether neural differences between family history and healthy control groups can predict a subsequent MDD diagnosis.

Despite these limitations, our study demonstrates that relative to healthy controls, individuals with a family history of MDD are associated with altered task-dependent vmPFC-cerebellar activity during a social cognition task. Previous research shows that the cerebellum plays a key role in processing social, affective and rewarding stimuli and is a region of interest in psychiatric illnesses, including MDD (Konarski et al., 2005). Evidence for neural alterations underlying social cognition in advance of a personal episode of MDD implies the possibility of early intervention and support that may mitigate later emergence of the disorder. Abnormal neural connectivity has been documented in other social disorders (Young et al., 2015) and may play a central role in the development of psychiatric illnesses (Zhang et al., 2015) and maladaptive behaviors (Diehl et al., 2018). From a clinical lens, the identification of neural alterations and its ability to establish a diagnosis or predict how an individual will respond to treatment remains unclear (e.g., Savitz et al., 2013). Yet, as research accumulates data detailing the mechanisms driving neural alterations, future work may more reasonably employ emergent technology—such as brain stimulation—to intervene (Diehl et al., 2018). Considering the limits MDD places on social cognition (Knight & Baune, 2018), addressing abnormalities in the underlying neural mechanisms of social cognition in particular lends itself to the development of treatments that facilitate social support and connection, a leading protective factor against future depressive episodes (Cruwys et al., 2014). Additional work must continue to investigate how the cerebellum connects with other regions across a variety of affective disorders to understand the full spectrum of the site's role in healthy and abnormal social cognition alike.

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