The structural and functional brain network in early- and later-onset major depressive disorder

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Abstract

Background: Major depressive disorder (MDD) is one of the most common psychiatric disorders for all ages. Gaps in neurobiological understanding of MDD across the lifespan hinder much needed diagnostic and treatment advances in the disorder. This study aimed to examine the structural and functional brain network in early- (age of onset < 30 years) and later-onset (age of onset ≥ 30 years) MDD using an existing and growing database at China Medical University (Shenyang, China).

Methods: A total of 476 participants [193 individuals with MDD and 276 healthy controls (HC)] who underwent resting state functional MRI (fMRI) and diffusion tensor imaging (DTI) were included in the study. A significant proportion of the sample was first episode (within first 2 years of illness onset) and/or medication naïve. Recently developed resting-state fMRI measures, amplitude of low frequency fluctuations (ALFF) and regional homogeneity (ReHo), were used to preliminarily examine the functional brain network in the early- and later-onset MDD groups, compared to their age matched HC. Fractional anisotropy (FA) was calculated using DTI to examine the structural brain network. Based on these analyses, the study approach was modified for more informative analyses. Subsequently, participants were divided into three age groups based on the established trajectory of white matter development: 13-21 years, 22-29 years, and 30-45 years. Distance-based functional connectivity (FC) and FA analyses were performed comparing MDD and HC in each age group.

Results: Significant alterations in ALFF and ReHo were found in later-onset MDD, compared to age matched healthy controls (HC), primarily in the cuneus. No significant differences were found between early-onset MDD and age matched HC. FA was significantly decreased in the corpus callosum and cingulum in early-onset MDD, compared to age-matched HC. No significant differences were found between later-onset MDD and age-matched HC.

Distance-based FC analyses revealed no significant differences between MDD and HC in ages 13-21 years. In ages 22-29 years, short range FC was significantly decreased in temporal regions and the cuneus in MDD, compared to HC, while significantly increased short range FC was shown in frontal regions. Medium/long range FC was significantly increased in limbic and parietal regions in MDD, compared to HC. Ultra-long range FC was significantly increased in frontal, limbic, and occipital regions. For ages 30-45 years, short range FC was significantly decreased in frontal and parietal regions in MDD, compared to HC. Medium range FC was significantly decreased in frontal regions and significantly increased in the cuneus in MDD when compared to HC. Ultra-long FC was significantly increased in right frontal region and bilateral cuneus. Significant FA increases were observed in the cerebellar vermis and hemisphere in MDD compared to HC for ages 13-21 years. For ages 22-29 years, significant FA decreases were found in the corpus callosum and cingulum. No significant FA differences were shown for ages 30-45 years. Specifically, significant FA, compared to HC.

Conclusions: Findings indicate alterations in the structural and functional brain network in MDD across adolescence to adulthood. They indicate a greater role of short range connections in adult MDD than adolescent MDD. They also support the potential presence of multiple neural trajectories in MDD across the lifespan.

Lay summary

Depression is a common mental illness across all ages. Worldwide, it affects approximately 350 million people. Despite improved recognition and treatment of depression, it continues to cause significant suffering and burden for individuals, their families, and society. Further advances in diagnosis and treatment of depression are needed but hindered by many unanswered questions about how depression works in the brain. What we do know: 1) There are brain differences between those with

depression and those without. 2) Brain networks are important in depression. 3) Brain changes may differ based on the age when depression first began. How the brain network differs across the lifespan in depression is unclear. Answers to this question could provide important insight for advancing diagnosis and treatment in depression, however the search for answers is challenging as it is unclear which MRI technique is most appropriate and reliable and what are the critical ages for the development of depression. In this study, we examined the structural and functional brain network in depression using different MRI techniques and age-based groupings. Our findings indicate 1) structural and brain network alterations across adolescence to adulthood, 2) short range network connections may have greater role in adult depression than adolescent depression, and 3) the possibility of multiple brain trajectories in depression based on age of illness.

Introduction

Major depressive disorder (MDD) is one of the most common psychiatric disorders across the lifespan. Despite improved recognition and treatment, MDD continues to cause significant burden for individuals, their families, and society. Further advances in diagnosis and treatment of MDD are needed; however gaps in understanding MDD neurobiology pose significant barriers. Mounting evidence indicates neural alterations in multiple brain systems in MDD, highlighting the need to understand the brain network in the disorder. Recently, different neuroimaging techniques have been developed to study the brain network including graph analysis; however which techniques are most appropriate and reliable remain unclear. Further, the brain undergoes characteristic shifting in growth and pruning that impact its structural and functional connectivity across the lifespan. Yet, studies have generally examined MDD without considering age of onset. Prior studies in MDD have used age 30 years old as a cut-off between early (childhood/adolescent) and adult-onset MDD; although there is no definitive evidence for what should be the age thresholds. Moreover, it is unclear how many neural trajectories exist in MDD based on age of onset. A recent study suggests that there may be multiple such trajectories within MDD[1].

We proposed to examine the structural and functional brain network in early- (age of onset < 30 years) and later-onset (age of onset $\geq$ 30 years) MDD using graph analysis. In the present study, we implemented different MRI methods and age-based groupings to examine the structural and functional brain network in MDD across the lifespan.

Methods

The work was performed as part of an ongoing collaboration between Washington University (WU) and China Medical University (CMU) and utilized an existing and growing CMU database of healthy controls (HC) and individuals with MDD ages 13 to 65 years old from Shenyang, China. A total of 476 participants (193 individuals with MDD and 276 HC) were included in the study and underwent resting state functional MRI (fMRI) and diffusion tensor imaging (DTI). FMRI was used to examine the functional brain network while DTI was used to examine the structural brain network. A significant proportion of the sample was first episode (within first 2 years of illness onset) and/or medication naïve as recruitment was targeted to these populations. The presence or absence of DSM-IV disorders was determined by consensus diagnosis of two trained psychiatrists using the Structured Clinical Interview for DSM-IV disorders. No participant had a history of substance abuse or dependence, neurological illness, head trauma with loss of consciousness over 5 minutes, significant medical disorders, or MRI contraindications. No HC participant had a first degree relative with an Axis I disorder. Resting state fMRI and DTI images were obtained at a single site at CMU using a 3.0-T GE Signa System (GE Signa, Milwaukee, Wisconsin, USA) with standard parameters. Informed consent was obtained from all participants. For participants under age 18 years, informed consent was obtained from their legal guardian and assent was obtained from the minor participant.

Preliminary analyses were performed using amplitude low frequency fluctuations (ALFF) and regional homogeneity (ReHo), two recently developed fMRI measures of regional neural activity at resting state. [ALFF measure the fluctuations in BOLD-fMRI signal intensity within a particular region; whereas ReHo measures temporal homogeneity of low frequency fluctuations (LFF) within the region.] DTI-based fractional anisotropy (FA) was also calculated and analyzed in these groups. [FA measures the directionality of a diffusion process and characterizes white matter microstructure (e.g., myelination).] For these analyses, participants were grouped as: young HC (aged < 30 years), older HC (aged $\geq$ 30 years), early-onset MDD (age of onset < 30 years), and later-onset MDD (age of onset $\geq$ 30 years), and MDD groups were compared to their age-matched HC group. The preliminary results led to reconsideration of several issues: 1) the validity and reliability of age of onset in the sample (primarily based on retrospective report by participant), 2) the potential for multiple neural trajectories within MDD across the lifespan, 3) the potential confounding effects of older age (> 45) on neural alterations, and 4) the potential for oversight when characterizing multiple networks as a single global network, as would occur with graph analyses. After consultation with other field experts, review of current literature, and consideration of related unpublished work at CMU, we determined that the originally proposed graph analysis was unlikely to yield additional findings. Graph analysis was consequently not performed, and we modified our study approach for potentially more informative analyses: 1) grouped based on age of scan instead rather than age of onset in MDD, 2) narrowed the age range of participants to ages 13-45 years, 3) account for evidence of multiple age-related neural trajectories in MDD, and 4) utilized a recently published technique for distance-based functional network analyses[1].

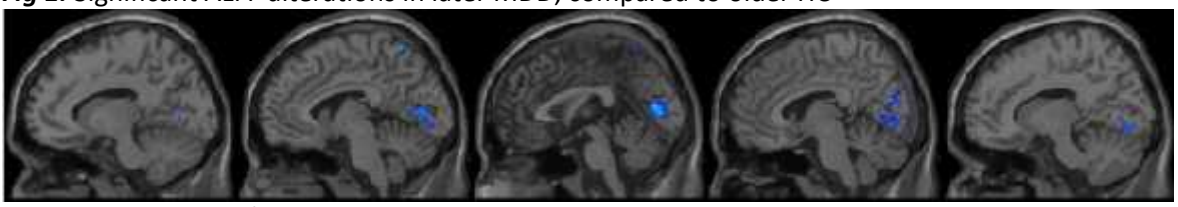
With the modified approach, participants were divided into three age groups based on established understanding of white matter (WM) development: 13-21 years (70 MDD and 52 HC), 22-29 years (40 MDD and 145 HC), and 30-45 years (83 MDD and 79 HC). Distance-based functional connectivity (FC) and FA analyses were performed comparing MDD groups with their age-matched HC group. For distance-based FC analyses, the Euclidean distance (d_{ij}), straight line distance, was calculated between voxel i and voxel j as an approximate anatomical distance of the FC between voxels. D_{ij} were divided into 18 bins ranging from 0 to 180 mm by 10 mm increments (e.g., bin 1 for d_{ij} 0 to 10 mm). Whole brain FC was then divided into the 18 distance bins based on their d_{ij}. For each bin, whole brain FC was compared between groups.

Statistically appropriate analyses were performed using significant p value as <0.05 with correction for multiple comparisons.

Results

Preliminary analyses: Significant differences in ALFF (Fig 1) and ReHo (Fig 2) were found in later-onset MDD, compared to older HC; no significant differences were found between early-onset MDD and young HC. ALFF was significantly decreased in the cuneus in later-onset MDD, however very few significant changes were noted across the brain as a whole.

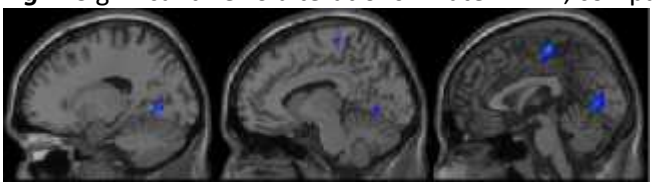
Fig 1. Significant ALFF alterations in later MDD, compared to older HC



Blue = decrease; red/orange = increase

A similar pattern was observed with ReHo in later MDD with significantly decreased ReHo in primary motor cortex and cuneus.

Fig 2. Significant ReHo alterations in later MDD, compared to older HC



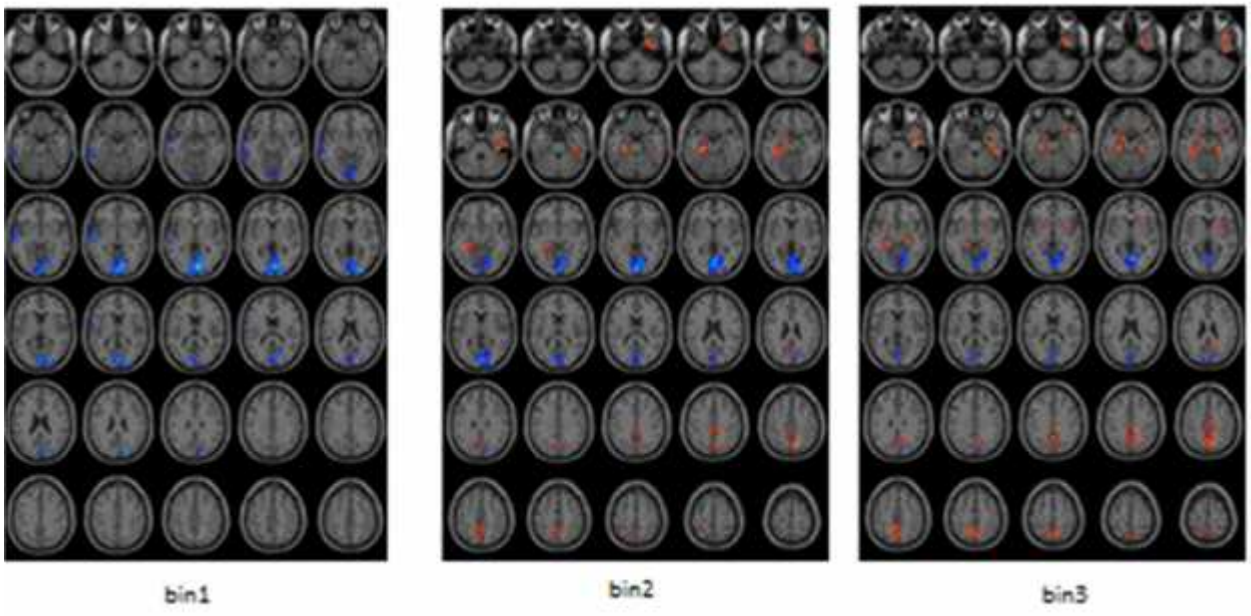
Blue = decrease; red/orange = increase

Significant differences in FA were observed in early-onset MDD, compared to young HC; no significant differences were found between later-onset MDD and older HC. FA was significantly decreased in the corpus callosum and cingulum in early-onset MDD, compared to young HC.

Distance-based FC across the three age groups: No significant differences were found between MDD and HC for ages 13-21 years. Significant differences were observed between MDD and HC for ages 22-29 years and 30-45 years. Specifically, for ages 22-29 years, decreased short range FC (bins 1-3) was found in temporal regions and the cuneus in MDD, compared to HC; while increased short range FC was shown in frontal regions (Fig 3). Medium/long range (bins 5-8) FC was significantly increased in limbic and parietal regions in MDD compared to HC. Ultra-long range FC (bins 15-16) was significantly increased in frontal, limbic, and occipital regions.

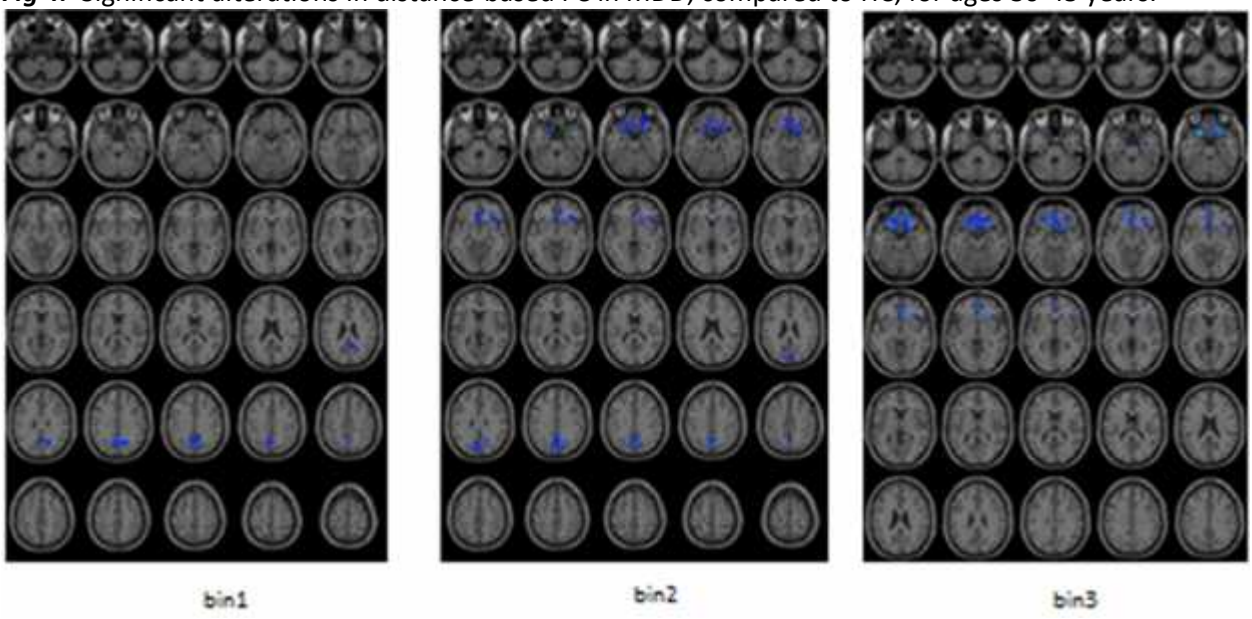
For ages 30-45 years, short range FC was significantly decreased in frontal and parietal regions in MDD, compared to HC (Fig 4). Compared to HC, medium range FC (bins 5 and 6) was significantly decreased in frontal regions and significantly increased in the cuneus in MDD. Smaller clusters of significant increases in ultra-long FC (bins 15 and 16) were noted in right frontal region and bilateral cuneus.

Fig 3. Significant alterations in distance-based FC in MDD, compared to HC, for ages 22-29 years.



Blue = decrease; red/orange = increase

Fig 4. Significant alterations in distance-based FC in MDD, compared to HC, for ages 30-45 years.



Blue = decrease; red/orange = increase

FA analyses across the three age groups: Significant FA differences were found between MDD and HC for ages 13-21 years and 22-29 years. No significant FA differences were shown for ages 30-45 years. Specifically, significant FA increases were observed in the cerebellar vermis and hemisphere in MDD, compared to HC, for ages 13-21 years (Fig 5). For ages 22-29 years, significant FA decreases were found in the corpus callosum and cingulum.

Fig 5. Significant FA alterations in MDD, compared to HC, for ages 13-21 years

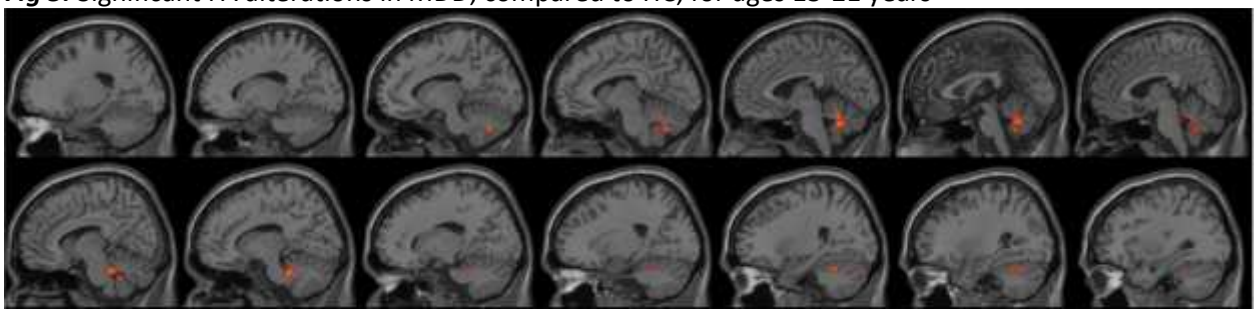


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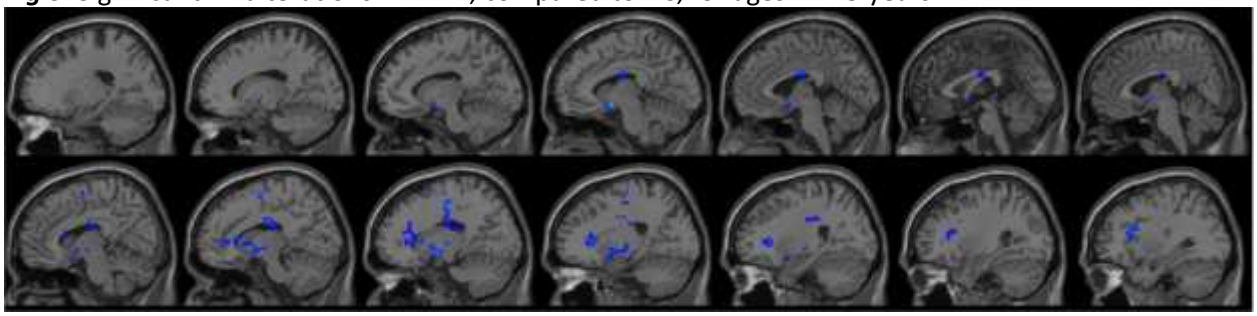
Fig 6. Significant FA alterations in MDD, compared to HC, for ages 22-29 years



Blue = decrease; red/orange = increase

Discussion

We originally proposed to examine the structural and functional brain network in MDD based on age of onset using graph analysis. Preliminary analyses indicated alterations in ALFF and ReHo in later-onset MDD while no significant differences were found between early-onset MDD and young HC. Significant alterations in FA were observed in early-onset MDD, compared to young HC. No significant differences were observed between later-onset MDD and older HC. While there were significant findings, the affected regions were limited, and the structural and functional findings were not consistent. Upon further consideration and consultation with other experts, we determined that graph analysis was unlikely to provide additional insight. Further, there were concerns whether age of onset and age 30 years were appropriate ways to categorize the sample. Consequently, we utilized different age-based groupings and network analysis technique to further examine the structural and functional brain network in MDD.

In the latter portion of the study, we examined distance-based FC and FA in MDD across three age groups that were determined based on the established trajectory for WM development: 13-21 years, 22-29 years, and 30-45 years. Distance-based FC across the lifespan is of great interest in light of the shifts in long and short range connections throughout life.[3] We found significant changes in short and medium range FC in MDD compared to HC for ages 22-29 years and 30-45 years. No significant alterations were observed in ages 13-21 years. The significant regions identified in these analyses have been previously implicated in emotional processing and regulation, and MDD. Interestingly, the pattern of distance-based FC alterations in MDD differed across age groups. Conceivably, this may represent different neural trajectories in MDD based on age of illness, particularly as there was a significant proportion of first episode individuals in this sample. However, longitudinal studies in purely first episode MDD sample would be more definitive on this matter. Unfortunately, while longitudinal follow-ups are being done in this sample, the available data is insufficient to perform the above analyses longitudinally at this time. The findings herein also implicate greater involvement of short range connections in functional network disruptions in adult MDD than adolescent MDD. From a structural network perspective, we found significant FA alterations in regions previously associated with mood, cognition, and MDD for MDD ages 13-21 years and 22-29 years. Again, we observed different patterns of structural network alterations in MDD across age groups. For ages 22-29 years, the regions of FA alterations in MDD are major WM tracts that interconnect the significant regions observed in the distance-based FC analyses. However, direct correlation between structural and functional findings is limited as FA reflects WM microstructure and does not indicate fiber types (e.g., short versus long range) within WM bundles.

In summary, we aimed to examine the structural and functional brain network in MDD based on age of onset. We originally proposed using graph analyses to accomplish these aims. Preliminary analyses were performed for a sample grouped based on age of onset before or after 30 years. These analyses had limited findings and raised several concerns, as well as indicated unlikelihood of additional insight using graph analyses. We modified our study approach for more informative analyses. These analyses support 1) greater involvement of short range connections in adult MDD than adolescent MDD, 2) different patterns of distance-based FC alterations in regions associated with emotional regulation and processing and MDD in MDD individuals across age groups of 13-21 years, 22-29 years, and 30-45 years, and 3) different patterns of altered structural connectivity in MDD across age groups of 13-21 years, 22-29 years, and 30-45 years. They also suggest the possibility of multiple neural trajectories based on age of illness in MDD. Altogether, the present findings implicate age-related differences in structural and functional brain network in MDD and underscore the importance of age considerations in MDD studies.

Future plans

We intend to continue more in-depth analyses of this sample, particularly those using distance-based techniques. The distance-based FC technique[2] presented herein can also calculate the number of connections within certain distance range and distance strength of particular nodes. Furthermore, other clinical and cognitive measures are available for this sample, as well as molecular measures such as plasma leptin level. Of note, there is mounting evidence of leptin's role in depression and its neural circuitry, including results from ongoing work at CMU (manuscript in preparation for one of several analyses related to leptin). Currently, we are in process of planning next steps with intent to apply for second year funding from the Longer Life Foundation. Additionally, first year funding has allowed for continued growth of our longstanding collaboration, and we are planning a R01 submission based on continued collaboration between WU and CMU in 2019.

References

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