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Graph theory approach for the structural-functional brain connectome of depression

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ABSTRACT

To decipher the organizational styles of neural underpinning in major depressive disorder (MDD), the current article reviewed recent neuroimaging studies (published during 2015–2020) that applied graph theory approach to the diffusion tensor imaging data or functional brain activation data acquired during task-free resting state. The global network organization of resting-state functional connectivity network in MDD were diverse according to the onset age and medication status. Intra-modular functional connections were weaker in MDD compared to healthy controls (HC) for default mode and limbic networks. Weaker local graph metrics of default mode, frontoparietal, and salience network components in MDD compared to HC were also found. On the contrary, brain regions comprising the limbic, sensorimotor, and subcortical networks showed higher local graph metrics in MDD compared to HC. For the brain white matter-based structural connectivity network, the global network organization was comparable to HC in adult MDD but was attenuated in late-life depression. Local graph metrics of limbic, salience, default-mode, subcortical, insular, and frontoparietal network components in structural connectome were affected from the severity of depressive symptoms, burden of perceived stress, and treatment effects. Collectively, the current review illustrated changed global network organization of structural and functional brain connectomes in MDD compared to HC and were varied according to the onset age and medication status. Intra-modular functional connectivity within the default mode and limbic networks were weaker in MDD compared to HC. Local graph metrics of structural connectome for MDD reflected severity of depressive symptom and perceived stress, and were also changed after treatments. Further studies that explore the graph metrics-based neural correlates of clinical features, cognitive styles, treatment response and prognosis in MDD are required.

1. Introduction

More than 9% of global population across diverse countries might suffer from major depressive episode and related hardships of role performance at least once in their lifetime (Kessler and Bromet, 2013). For better understanding of the neural correlates of clinical symptoms, treatment response, and disease prognosis for major depressive disorder (MDD), brain magnetic resonance imaging (MRI) have been widely used. Previous neuroimaging studies have reported between-group differences of brain inter-regional 1) structural connections by way of the white matter tracts and 2) coherence of time-varying fluctuations in functional brain activation in MDD compared to healthy controls (HC) or other psychiatric disorders. On the contrary, distribution of inter-regional connections across the whole brain and relative strength of local region-to-whole brain connections can be shown not by the comparisons of each connection strengths but by the global and local graph metrics (Fig. 1) (Bullmore and Sporns, 2009).

1.1. Brain white matter-based structural connectivity studies in MDD: unmet needs

Structural connectivity of brain refers to the physical interconnection of regional brain areas by way of the white matter tracts. Degree of the structural integrity of brain white matter tracts are measured using the fractional anisotropy (FA) values, among others. Higher FA value reflects stronger structural integrity of brain white

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matter tract which connects different brain regions. A recent multi-site study that examined structural integrity of white matter tracts using diffusion tensor imaging data gathered from 20 cohorts showed reduction of FA values in MDD ($n = 1305$) in corona radiata and corpus callosum compared to HC ($n = 1602$) (van Velzen et al., 2019). Moreover, a recent meta-analysis of diffusion tensor imaging studies for unmedicated adult MDD reveals lowered FA value of right cerebellar tracts, body of the corpus callosum, bilateral superior longitudinal fasciculus III, and arcuate fasciculus in MDD compared to HC (Jiang et al., 2017). Another recent meta-analysis of diffusion tensor imaging for adolescent MDD patients demonstrates lowered FA values at cingulum bundle and anterior thalamic radiation compared to HC (Lichenstein et al., 2016). Collectively, recent studies for MDD found lowered FA values across widespread brain white matters tracts including corona radiata, corpus callosum, superior longitudinal fasciculus, cingulum bundle, arcuate fasciculus, and anterior thalamic radiation in MDD compared to HC. Of note, graph theory metrics calculates the balance between the 1) network segregation clustered as sub-regions with tighter physical connections versus 2) network integration across all of the brain region by way of the direct and indirect physical connections. Graph theory metrics also reveal the distribution of brain white matter tracts with lowered structural integrity within the whole brain for MDD compared to HC.

1.2. Resting state functional connectivity studies in MDD: unmet needs

Resting state functional connectivity (Table 1) reflects the inter-regional similarity in the patterns of time-varying fluctuations of brain functional activations during task-free status. Compared to HC, resting state functional connectivity of MDD shows 1) weaker intra-module functional connectivity of frontoparietal network, 2) stronger intra-module functional connectivity of default mode network, and 3) stronger inter-module functional connectivity between the components of frontoparietal network and components of default mode network (Kaiser et al., 2015). On the other hand, inter-modular functional connectivity 4) between posterior default mode network versus salience network and 5) between anterior default mode network component versus limbic affective network are attenuated in MDD compared to HC (Kaiser et al., 2015). In summary, changed strengths of resting state functional connectivity within the default mode network in addition to default mode components versus frontopareital-salience-limbic networks are found. Further, graph theory approach for the resting state functional connectivity of MDD calculates the level of balance between the 1) network segregation as modules comprised of brain regions that show selectively higher coherence for the time-varying fluctuations of functional activation versus 2) network integration by way of the mediating brain regions that show tighter functional connections with multiple modules) and estimate the network efficiency of information transfer.

1.3. Graph theory: how to decipher the organizational styles of neural underpinning in MDD?

Graph theory approach is a mathematical framework to model the pairwise associations between components comprising a network. By estimating the global and local network metrics for the structural and functional connectome (Rubinov and Sporns, 2010), distribution of white matter-based physical connections and time-varying fluctuations of functional activations during resting state across the whole brain can be characterized for MDD (Gong and He, 2015). First, global network metrics reflects the degree of balance between the 1) averaged efficiency of reaching other brain regions within a network versus 2) selective clustering of network components as triplets or modules (Kambeitz et al., 2016; Suo et al., 2018) (Fig. 1A). For the brain structural connectome, characteristic path length and global efficiency values demonstrate the degree of physical connectedness among the different brain regions by way of the white matter tracts. In the functional connectome, these global metrics of network integration are related to the degree of coherence in the time-varying oscillations of functional brain activations among the different brain regions. In addition, clustering coefficients and modularity values calculated from the structural

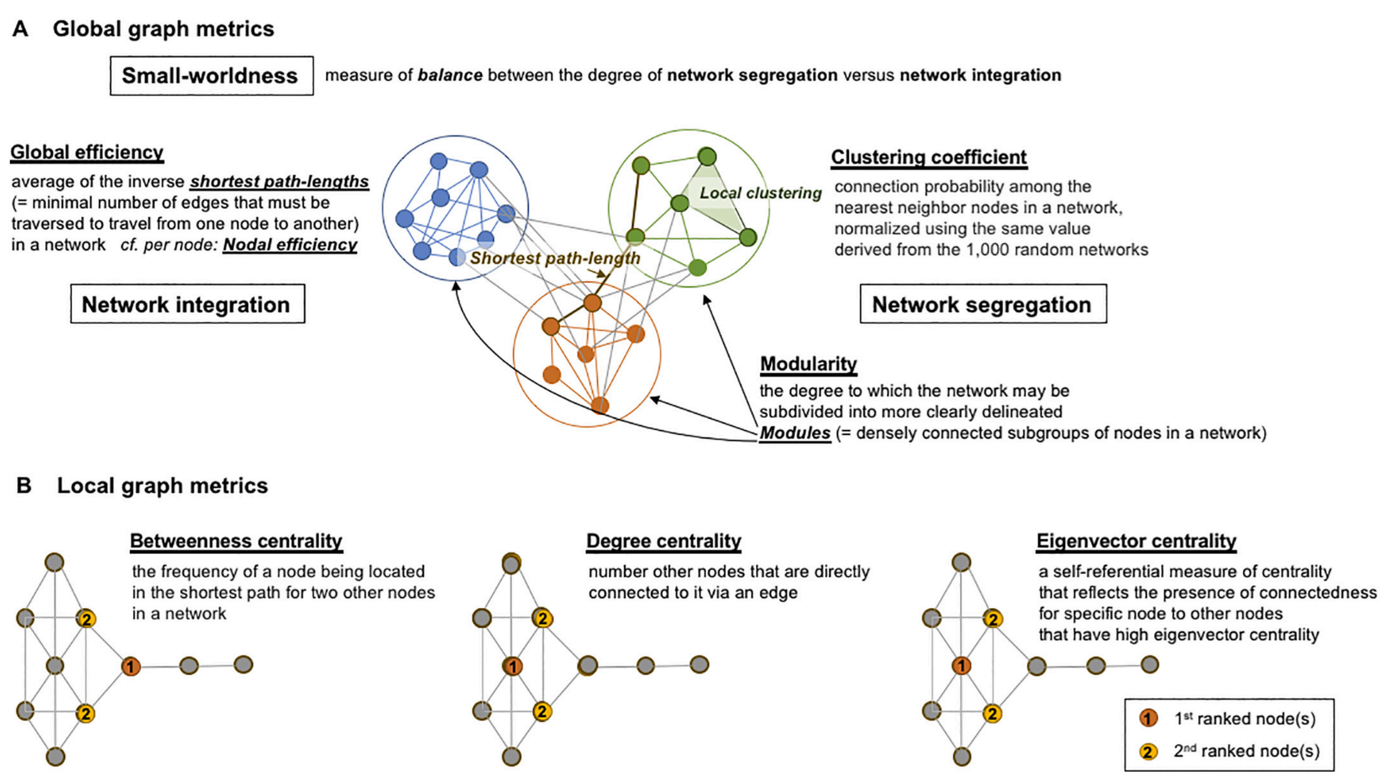

Fig. 1. (A) Global and **(B)** local graph metrics (modified from Fig. 1 of Yun et al. (2020)).

Table 1
Sub-network communities of functional brain connectome.

Sub-network communities	Regional brain components	Cognitive roles
Default mode network	Posterior cingulate cortex	Internally-oriented attention
	Ventromedial prefrontal cortex	Self-referential thoughts
	Inferior parietal lobule	Autobiographic memory
	Middle temporal gyrus	Introspective cognition
	HIppocampus	
Fronto-parietal network	Dorsolateral prefrontal cortex	Goal-directed attentional control
	Posterior parietal cortex	Reasoning and decision making
	Mid-cingulate	Emotional regulation
Salience network	Anterior insula	Monitoring for salient events
	Dorsal anterior cingulate cortex	Interoceptive awareness
	Ventrolateral prefrontal cortex	Motivational behavior
	Putamen	
Dorsal attention network	Intraparietal sulcus	Top-down attentional selection
	Superior parietal lobule	
	Frontal eye field	
Ventral attention network	Temporo-parietal junction	Stimulus-driven attentional control
	Ventral prefrontal cortex	Reorienting to unexpected events
		Response to contextual cues
Affective (limbic) network	Amygdala	Emotional processing
	Nucleus accumbens	
	Orbitofrontal gyrus	
	Subgenual anterior cingulate	
	Inferior temporal gyrus	
Subcortical network	Thalamus	–
	Caudate	
	Putamen	
Sensorimotor network	Pre/para/postcentral gyri	–
	Superior temporal gyrus	
Visual network	Fusiform gyrus	–

connectome reflect the physical integrity of cortical-subcortical neural circuits which are segregated from other brain regions. In case of the functional connectome, presence of distinctive functional modules or communities is related to the higher values of these global metrics of network segregation. As a matter of fact, heuristic clustering algorithms could estimate the modules or communities, each comprised with brain regions that show higher concordance in fluctuating patterns of time-varying functional activations (Crossley et al., 2016; Sha et al., 2018). On the other hand, local graph metrics of centrality show relative influence of each brain regions within given network. Degree centrality and nodal strength describe number of connected components and summated strengths of connections between each brain region and other brain regions, respectively. Importance of each brain region within a network also can be measured using the eigenvector centrality related to the number of connected brain regions with higher centrality values and using the betweenness centrality that reflects chances of each region becoming a shortcut component that connects different brain regions (Farahani et al., 2019) (Fig. 1B). Finally, small-worldness of the structural connectome is related to the efficiency of information transfer among the different regions by way of the shortcut connections that mediate brain regions with higher centrality values.

1.4. Aims & search strategies of the current review

Therefore, the current review aimed to demonstrate the organizational characteristics of brain structural and functional connectomes in MDD compared to HC, association with clinical manifestation of MDD, in addition to the treatment response and disease prognosis. Using the search engine of Pubmed (https://pubmed.ncbi.nlm.nih.gov/), we firstly applied keywords of "functional, brain, graph, depression" for the Section 2 (graph theory approach for the functional connectome of MDD) and "diffusion tensor, network, depression" for the Section 3 (graph theory approach for the structural connectome of MDD), respectively. Of note, we applied the term of "graph" instead of "network" in the searching of candidate articles for Section 2 was for excluding other studies that examined resting state functional connectivity network of MDD by way of other analytic techniques such as seed-based connectivity, independent component analysis, among others (Taylor et al., 2021). With manual reviews for all of the articles retrieved and selected relevant articles 1) applied graph theory approach and calculated global and local graph metrics 2) from either diffusion tensor imaging or resting state T2* imaging scans 3) acquired from HC and patients with primary diagnosis of MDD (including the late-life depression and recurrent MDD) 4) were published during 2015 and 2020.

2. Graph theory approach for the functional connectome in MDD

2.1. Global graph metrics of functional connectome in MDD compared to HC

Global network organization of the resting state functional connectivity networks (rs-FCN) in MDD varies according to the onset age and medication status. Most of all, level of balance between the network segregation and network integration for the rs-FCN in MDD is comparable to HC (Borchardt et al., 2015; Borchardt et al., 2016; Dong et al., 2019; Wang et al., 2016b; Weng et al., 2019; Yin et al., 2016; Yu et al., 2020; Zhang et al., 2020). Also, a few studies reported lowered small-worldness of the rs-FCN for MDD in their thirties (Li et al., 2017b) and patients with late-life depression (LLD) with pharmacotherapy (Li et al., 2015). Network segregation of the rs-FCN measured using the global metrics of clustering coefficients is weaker in adult MDD compared to HC, both during the depressive (Li et al., 2017b; Ma et al., 2019; Weng et al., 2019; Zhang et al., 2020) and euthymic (Dong et al., 2019; Yao et al., 2019) phases. Specifically, clustering coefficients of the rs-FCN in adult MDD with pharmacotherapy are lower than HC (Borchardt et al., 2016). Conversely, the rs-FCN of unmedicated adult MDD (Borchardt et al., 2015; Dvorak et al., 2019; He et al., 2016; Wang et al., 2017b; Yu et al., 2020) shows comparable network segregation with HC. Likewise, the rs-FCN of LLD show comparable network segregation to HC (Li et al., 2015; Wang et al., 2016a; Wang et al., 2016b; Yin et al., 2016). Further, the rs-FCN of LLD patients with pharmacotherapy reveal even higher network segregation compared to HC (Mak et al., 2016). In short, less prominent clustering among the different brain regions for the time-varying fluctuations of functional activations at resting state compared to HC might be a characteristic of adult MDD with pharmacotherapy.

Network integration of rs-FCN for adult MDD estimated using the global efficiency and characteristic path length differs according to the onset age. Not only for medicated (Borchardt et al., 2016) but also for unmedicated (Chen et al., 2017; He et al., 2016; Wang et al., 2016a; Ye et al., 2015; Yu et al., 2020) status, network integration estimated by way of the global efficiency and characteristic path length is comparable to HC in MDD. For first episode MDD in their early 20s, network integration is similar between HC and MDD both in depressive and remitted phases (Dong et al., 2019). On the contrary, compared to HC, network integration of the rs-FCN is weaker in adult-onset MDD aged between late 20s and early 30s, both in medicated (Zhang et al., 2020) and unmedicated (Wang et al., 2017b) status. Further, increased network integrity of the rs-FCN reflected in the higher global efficiency and shorter characteristic path length compared to HC is found from MDD in their 30s (Li et al., 2017b), MDD in their 40s (Weng et al., 2019), and depressive patients with seasonal affective disorder in their early 40s (Borchardt et al., 2015). Collectively, network integration of the resting state functional connectome in adult MDD, which was intact at first depressive episode, fluctuates along suffer from the multiple depressive episode and prolonged illness duration. In cases of LLD, network integrity of the rs-FCN is reduced compared to HC both in depressive and remitted phases (Li et al., 2015; Wang et al., 2016b; Yin et al., 2016; Zhu et al., 2018).

2.2. Community assignment of functional connectome in MDD compared to HC

Compared to HC, less tight inter-regional clustering among the members comprising each functional modules or communities (Table 1) of the rs-FCN for MDD is reflected in the lower modularity value. Of note, weaker intra-modular resting state functional connections within the default mode components and limbic network components compared to HC are found from unmedicated MDD in their early 30s with illness duration of 3.5 years (Wang et al., 2017b). Further, when illness duration is prolonged and unmedicated MDD reaches in their late 40s, exclusive functional clustering among the limbic network components of amygdala, hippocampus, and parahippocampal gyrus during resting state are lost (Yu et al., 2020). Likewise, strengths of the intra-modular functional connections among the components of default mode network are still weaker compared to HC for the res-FCN of remitted LLD in their late 60s with illness duration of 3.1 years (Zhu et al., 2018). On the contrary, for unmedicated MDD in their early 30s and with illness onset of between late 10s and early 20s, graph metrics of 'entropy' that reflects a distribution of the inter-regional functional connection strengths among the default mode network components is comparable with HC (Jacob et al., 2019). On the other hand, for adolescent MDD, intra-modular functional connectivity of salience network and attention network are weaker compared to HC (Sacchet et al., 2016). Collectively, weaker inter-regional functional clustering at resting state within the default mode network and limbic network is a marker of adult MDD with onset age of mid 20s and later (including the LLD). For MDD with younger onset age of adolescence and early 20s, changed strengths among the components of functional modules other than default mode network might be contributors of lowered modularity for the rs-FCN.

Altered strengths of inter-modular functional connections in the rs-FCN of MDD compared to HC also vary according to the onset age of MDD. For adult MDD, inter-modular functional connections between the components of dorsal attention network versus components of ventral attention, limbic, and subcortical networks, between the components of visual network versus components of limbic, subcortical, and default mode networks, and between the components of frontoparietal network versus components of ventral attention and subcortical networks are increased compared to HC (Ma et al., 2019). Also, compared to schizophrenia, inter-modular resting state functional connectivity between the frontal-insular portion of salience network and posterior-parietal components of default mode network are stronger for adult MDD (Shao et al., 2018). On the contrary, the rs-FCN of MDD in adolescence demonstrates attenuated inter-modular functional connections between the salience network versus components of frontoparietal and sensorimotor networks, between the components of default mode network versus attention and sensorimotor networks, and between the components of frontoparietal network versus attention network, compared to HC (Sacchet et al., 2016). In short, the resting state functional connections among the brain regions comprising different functional modules of the rs-FCN compared to HC are tighter for adult MDD and looser for adolescent MDD. Of note, regarding the resting-state functional modules of salience, limbic, or default mode networks, attenuated intra-modular functional connections for adolescent MDD and reduced inter-modular functional connections for adult MDD are found compared to HC.

2.3. Local graph metrics of functional connectome in MDD compared to HC

Reduced intra-module and inter-module functional connectivity of default mode network (as shown in the **Section 2.2.** above) for adult MDD during resting state is also found at the level of local graph metrics. In other words, a summated value of functional connections between precuneus and neighboring brain regions within the default mode network is reduced compared to HC in the rs-FCN of MDD in their late 20s (Wang et al., 2017a). In addition, brain regions comprising the anterior and posterior parts of default mode network reveal lowered centrality values in the rs-FCN of adult MDD in their 30–40s and of LLD compared to HC. First, summated values of the functional connection strengths or nodal strengths between precuneus, posterior cingulate cortex, or inferior parietal lobule versus other brain regions during resting state are lowered for adult MDD in their early 30s and remitted LDD in their late 60s, compared to HC (Shi et al., 2020; Wang et al., 2017b; Zhang et al., 2020; Zhu et al., 2018). Second, number of the functional connections between the anterior cingulate, middle temporal, or parahippocampal gyri versus other brain regions with significant connection strengths, calculated using the degree centrality, are smaller for the rs-FCN of MDD in their 40's compared to HC (Sheng et al., 2018).

Among the ventral brain regions, not only the efficiency of information transfer between insula and other brain regions but also the importance of insula as a key mediator among the inter-regional functional connections are lowered for the rs-FCN of MDD in their early 40's with onset age of early 30's (Dvorak et al., 2019) and remitted LLD in their late 60's (Wang et al., 2016b) compared to HC. In case of inferior frontal gyrus, although local graph metrics of nodal efficiency and nodal strength values are smaller in adult MDD with onset age from early 30's (Shi et al., 2020) to late 30's (Yu et al., 2020) and in remitted LLD in their late 60's (Wang et al., 2016b), value of betweenness centrality is higher than HC (Dvorak et al., 2019). These results imply possible reduced mediation by the salience network component of insula and increased mediation by the ventral attention network component of inferior frontal cortex among the inter-regional functional connections for adult MDD and LLD during resting state. On the other hand, tighter inter-modular functional connections between limbic network and other brain regions for the rs-FCN of adult MDD with onset age of mid 20's or 30's are contributed from the stronger nodal strength and degree centrality values of inferior temporal gyrus and subcallosal-subgenual cingulate cortices as well as the lower nodal efficiency/strength values of temporal pole compared to HC (Amiri et al., 2019; Shi et al., 2020; Wang et al., 2017b; Wu et al., 2016).

For the dorsal brain regions, nodal strength and degree centrality of posterior parietal cortex is reduced in adult MDD compared to HC, both in depressive and remitted mood phases (Dong et al., 2019; Sheng et al., 2018; Shi et al., 2020). Moreover, intra-modular functional connections between the dorsolateral prefrontal cortex and other regions of frontoparietal network are weaker in MDD compared to HC (Ma et al., 2019). Regarding the inter-modular functional connectivity, lowered value of summated functional connection strengths and reduced number of functional connections between dorsolateral prefrontal cortex and other brain regions compared to HC are found in the rs-FCN of adult MDD both during depressive and remitted phases (Dong et al., 2019; Sheng et al., 2018; Shi et al., 2020). On the contrary, functional connections between the dorsolateral prefrontal cortex and subcortical regions during resting state are stronger in MDD compared to HC (Ma et al., 2019). Further, higher betweenness centrality of dorsolateral prefrontal cortex within the rs-FCN of MDD compared to HC shows higher involvement of dorsolateral prefrontal cortex as a mediator of inter-regional resting state functional connections in MDD (Dvorak et al., 2019). In short, in spite of the reduced functional connections with other regions in general, selectively spared or increased functional connections between the dorsolateral prefrontal cortex versus subcortical and other regions with higher inter-regional functional connections preserve the influence of frontoparietal network within the rs-FCN of MDD.

Values of the local graph metrics regarding the components of subcortical, sensorimotor, and visual networks comprising the rs-FCN of adult MDD vary according to the onset age. Most of all, inter-modular functional connections between the thalamus versus components of sensorimotor network are stronger for MDD in their mid-20's with onset age of early 20's, compared to HC. Also, higher nodal strength and degree centrality of the thalamus, caudate, precentral gyrus, and middle occipital gyrus compared to HC are found in the rs-FCN of adult MDD with onset age between the mid 20's and early 30's (Amiri et al., 2019; Shi et al., 2020; Wang et al., 2017b; Wu et al., 2016; Zhang et al., 2020). On the contrary, nodal efficiency of putamen, pallidum, cuneus, superior and middle occipital gyri are lowered in the rs-FCN of remitted LLD in their late 60's and middle-aged MDD with onset age of late 30's compared to HC (Wang et al., 2016b; Yu et al., 2020).

2.4. Graph metrics of functional connectome associated with clinical features in MDD

Local centrality values of the default mode, frontoparietal, limbic, and subcortical networks in addition to the global network efficiency are related to the intensity of depressive mood, ruminative thoughts, suicidal ideation, and neurocognitive functioning of MDD. Most of all, severity of depressive symptom of MDD in their 20s–30s is associated with weaker nodal strength, nodal efficiency, or degree centrality of default mode (Gong et al., 2018; Shi et al., 2020), frontoparietal (Dong et al., 2019; He et al., 2016), and limbic (Wu et al., 2016) networks. Of note, ruminative thoughts (repetitive focused thoughts of one's distress and negative mood status with a self-critical nature) is more intense for MDD with weaker nodal strength of default mode network (Jacob et al., 2019). Further, suicidal ideation of MDD is associated with weaker nodal strength and nodal efficiency values of thalamus and components of limbic and frontoparietal networks (Kim et al., 2017). Finally, for the cognitive performance of remitted LLD in their late 60s with illness duration of 3 years, positive correlations between the global efficiency versus processing speed, delayed recall of auditory verbal memory, working memory, and executive function of set-shifting are found (Yin et al., 2016; Zhu et al., 2018). Moreover, higher nodal efficiency of the putamen is related to the better episodic memory and faster processing speed of remitted LLD (Wang et al., 2016b).

Illness burden of MDD such as duration of illness and number of mood episodes are reflected in the local centrality values of the default mode, frontoparietal, and limbic network components and putamen in addition to the changed inter-modular functional connectivity of default mode, visual, and salience networks. For first-episode MDD in their early 20s, nodal efficiency of parahippocampal gyrus is higher compared to HC and is more increased after the remission of first major depressive episode (Dong et al., 2019). On the contrary, longer illness duration and number of depressive episodes in MDD are associated with weaker nodal efficiency of default mode network (Gong et al., 2018), higher nodal efficiency and degree centrality of putamen and nucleus accumbens (Brandl et al., 2018), in addition to the stronger inter-modular functional connectivity between the components of default mode network and visual network (Ma et al., 2019). For middle-aged MDD with illness onset at their 20s, residual symptoms of depressive mood and irritability are related to the higher local efficiency of frontoparietal network (Servaas et al., 2017) and weaker inter-module functional connectivity between the salience network and other brain regions (Servaas et al., 2017).

2.5. Graph metrics of functional connectome associated with treatment response in MDD

Response for pharmacotherapy with antidepressants in MDD in their 30s–40s with illness duration less than 6 years is associated with centrality and intra-modular connectivity values of default mode network. In addition, degree of lowered nodal efficiency for default mode network component of hippocampus in MDD compared to HC predicts more reduction of depressive symptoms after the pharmacotherapy with antidepressants for 2 weeks (Gong et al., 2018). On the contrary, stronger intra-modular connectivity of the salience network component at baseline is associated with more reduction of depressive symptoms in response to the placebo administration in MDD (Sikora et al., 2016). After the 8 week-length pharmacotherapy with escitalopram for first-episode MDD, nodal strength values of default mode components and thalamus are increased (An et al., 2017). Of note, improvement of depressive symptom after the pharmacotherapy is proportional to the magnitude of nodal strength increment for posterior cingulate cortex (An et al., 2017). Further, after the pharmacotherapy with antidepressants for 8–12 weeks, degree centrality values of the default mode network components in MDD become comparable to those of HC (Sheng et al., 2018). Also, pharmacotherapy with antidepressants for 8–12 weeks results in increased intra-module connectivity of the limbic network compared to baseline (An et al., 2017).

Response to non-pharmacological treatment for adult MDD patients is related to the global network integrity in addition to the inter-modular connectivity or local centrality value of ventral attention, salience, and sensorimotor networks. First, greater improvement of depressive symptoms after 12 weeks of cognitive behavioral therapy is associated with reduction of the inter-modular connectivity between the ventral attention network and other regions in unmedicated MDD (Yang et al., 2018). Second, better treatment response for the accelerated intermittent theta burst stimulation (aiTBS) targeting the left dorsolateral prefrontal cortex is related to the higher global network integration measured using the global efficiency and clustering coefficient of pharmacotherapy-resistant MDD for selective serotonin reuptake inhibitor at baseline (Klooster et al., 2019). In addition, treatment-related increment of the betweenness centrality value for the left supplementary motor area after the aiTBS shows positive correlation with degree of depressive symptom reduction in MDD (Klooster et al., 2019). Third, stronger intra-module connectivity of salience network at baseline is predictive of more reduction of depressive symptoms for MDD in response to the 10 Hz-repetitive transcranial magnetic stimulation (rTMS) delivered at left dorsolateral prefrontal cortex (Fan et al., 2019).

3. Graph theory approach for the structural connectome in MDD

3.1. Global & local graph metrics of structural connectome in MDD compared to HC

Structural integrity of the brain white matter tracts measured using the fractional anisotropy (FA) values are lowered in MDD in their mid-30's with illness duration of 2.3 years compared to HC for overall network strength (Zheng et al., 2019) and specifically at corpus callosum and corona radiata (van Velzen et al., 2019). On the other hand, in the brain white matter-based structural connectome, two different brain regions are considered as structurally connected when multiple white matter fibers with sufficient FA values are reconstructed by way of the deterministic or probabilistic tractography. Global graph metrics which measure the distributed patterns of the white matter tracts regarding the FA values and number of white matter fibers that connect two different brain regions are spared for adult MDD but impaired in LLD. In other words, for structural connectome of adult MDD in their mid-30's with onset age between mid-20's and early 30's, degrees of network integration calculated by way of the global efficiency and network segregation measured using the clustering coefficient are similar to HC (Yao et al., 2019; Zheng et al., 2019). On the contrary, in remitted LLD as well as patients with post-stroke depression in their late 60's, network segregation and network integration of structural connectome are lowered compared to HC and non-depressive post-stroke patients, respectively (Wang et al., 2019; Xu et al., 2019).

In spite of the spared global network integration and segregation for the structural connectome of adult MDD, local graph metrics demonstrates not only higher structural connections of thalamus and temporal cortices but also lowered structural connections of medial temporal-parietal and dorsolateral prefrontal cortices with other brain regions compared to those of HC. For the structural connectome of adult MDD in their mid-30's, capacity of possible information transfer by way of the white matter tracts measured using the local graph metrics of degree centrality and nodal efficiency are higher than HC for the thalamus, inferior-middle-superior temporal gyri, lingual and precentral gyri (Zheng et al., 2019). On the contrary, nodal efficiency of the adult MDD structural connectome is also lowered compared to HC in other regions of the default mode, visual, sensorimotor, and frontoparietal networks including the parahippocampal and Heschl's gyri, inferior parietal gyrus, precuneus, middle occipital gyrus, supplementary motor area, paracentral gyrus, and dorsolateral prefrontal cortex (Yao et al., 2019).

Further, in the structural connectome of remitted LLD in their late 60's, lowered nodal efficiency values compared to HC are found in the precuneus, superior and middle occipital gyri, pericalcarine cortex, insula, inferior frontal cortex, dorsolateral prefrontal cortex, and in subcortical brain regions of thalamus, putamen, and caudate nucleus (Wang et al., 2019). Likewise, local graph metrics of degree centrality and nodal efficiency calculated from the structural connectome of post-stroke depression in their mid-60's are lower than non-depressive post-stroke patients for brain regions of superior-middle frontal cortices, middle temporal cortex, posterior cingulate cortex, and amygdala (Xu et al., 2019). Lowered global and local graph metrics of structural connectome in remitted LLD as well as patients with post-stroke depression reflect general attenuation of physical connectedness by way of the white matter tract compared to HC.

3.2. *Graph metrics of structural connectome, stressors, and clinical features of MDD*

Global and local graph metrics of structural connectome are influenced by exposure to higher perceived stress and maltreatment. For the structural connectome of adolescent MDD, higher level of perceived stress is related to the attenuated age-related increment of summated structural connection strengths between the right caudate and other regions including the dorsolateral prefrontal cortex (Tymofiyeva et al., 2017). At early adulthood, regardless of the prevalence of mood disorder, prior exposure to the moderate-to-severe level of maltreatment is associated with the lowered global efficiency of structural connectome at early adulthood, compared to those with no-to-mild childhood maltreatment (Ohashi et al., 2017).

Degree of white matter tract-based physical connections between the components of limbic and default mode networks versus other regions are associated with severity of mood symptoms and could possibly modulate the influence of environmental factors to mood symptoms. Of note, higher nodal efficiency values of left inferior pars triangularis and amygdala in the structural connectome mediate positive associations between the numbers of exposure to maltreatment and severity of depressive or anxiety symptoms (Ohashi et al., 2019). In other words, tighter inter-regional physical connections by way of the white matter tracts might be a facilitator in propagating the impact of childhood maltreatment between the limbic components of left pars triangularis and amygdala and other brain regions. Moreover, severity of depressive symptoms for adult MDD in their mid-30's and onset age of late 20's is proportional to the lowered nodal efficiency of precuneus, middle occipital gyrus, and Heschl's gyrus (Yao et al., 2019). In contrast, higher local graph metrics of precuneus and fronto-temporal regions calculated from the structural connectome are associated with stronger stress-resilience characteristics of religiousness and spirituality for non-symptomatic adults in their early 30's with familial loading of MDD (Li et al., 2019).

For MDD with later onset age of 50's and 60's, changed values of the local and global graph metrics calculated from the structural connectome are related to the cognitive symptoms. First, intensity of suicidal ideation reported from adult MDD during the second depressive episode in their mid-50s is positively correlated with the betweenness centrality of dorsolateral prefrontal cortex (Myung et al., 2016). Second, lowered values of global network integrity calculated as global efficiency and values of network segregation measured as clustering coefficient for the structural connectome of remitted LLD in their late 60's are proportional to the slower processing speed (Li et al., 2017a).

3.3. *Graph metrics of structural connectome versus treatment response and prognosis of MDD*

Local graph metrics of brain regions comprising the default mode and salience networks reflect the different mood phases of active MDD episode and remitted phase. In the classification of MDD in their late 30's as active depressive phase versus remission using the support vector machine, key classifiers of remitted MDD are restored strengths of functional connections compared to HC for the intra-module connectivity between the default mode network components of precuneus and inferior parietal lobule, between the salience network components of insula and middle frontal gyrus, in addition to the inter-module functional connection between precuneus and superior temporal gyrus (Qin et al., 2015).

Local centrality values of superior and inferior frontal cortices calculated from the structural connectome of MDD are associated with both treatment-related changes and disease prognosis. First, 12 week-length pharmacotherapy with selective serotonin reuptake inhibitor for adults in their late 20's with diagnosis of mood or anxiety disorder(s) including MDD results in increment of betweenness centrality for superior frontal gyrus and decrement of betweenness centrality for inferior orbital frontal gyrus (Thomas et al., 2020). Second, a subset of MDD patients with lowered nodal efficiency of left inferior frontal gyrus compared to HC are prone to be converted into bipolar disorder within next 7 years (Liu et al., 2018). This study demonstrated a possible use of graph metrics calculated form the structural connectome of MDD as biomarker of disease prognosis.

4. Discussion

4.1. *Summary of the current study findings*

By reviewing the recently published neuroimaging studies (during 2015–2020) that applied graph theory approach to the diffusion tensor imaging data or functional brain activation data acquired during task-free resting state, the current study explored the organizational style of brain structural and functional connectome for MDD. First, global network organization of the rs-FCN in MDD varies with the onset age and medication status. Attenuation of the resting state functional clustering among the different brain regions compared to HC might be a characteristic of adult MDD with pharmacotherapy. Network integration of rs-FCN for adult MDD estimated using the global efficiency and characteristic path length was intact at first depressive episode but fluctuates along the trajectory of multiple depressive episode and prolonged illness duration. In cases of LLD, network integrity of the rs-FCN is reduced compared to HC both in depressive and remitted phases. For the white matter tract-based structural connectome, the global graph metrics of network integration measured using the global efficiency and network segregation calculated using the clustering coefficient are spared for adult MDD. On the contrary, in remitted LLD and patients with post-stroke depression, network segregation and integration of structural connectome are impaired.

Second, there is lower functional integrity of the default mode and limbic networks in MDD compared to HC. Weaker inter-regional functional clustering at resting state within the default mode network and limbic network as well as lowered local graph metrics of the precuneus, posterior cingulate cortex, inferior parietal lobule, anterior cingulate, middle temporal, and parahippocampal gyri is a marker of adult-onset MDD and LLD. In spite of the spared global network integration and segregation for the structural connectome of adult MDD, local graph metrics demonstrates lowered structural connections of medial temporal-parietal and dorsolateral prefrontal cortices with other brain regions compared to those of HC. For MDD with onset age of adolescence and early 20s, attenuated functional connections among the brain regions comprising salience network as well as between the components of salience network and other functional modules are found.

Third, depressive symptom patterns and illness duration differentially affect local network metrics. For the rs-FCN of MDD, illness duration, number of depressive mood episodes, severity of depressive mood, ruminative thoughts, suicidal ideation, and neurocognitive functioning are associated with values of local graph metrics for the components of default mode, frontoparietal, limbic, and subcortical networks and changed inter-modular functional connectivity of default mode, visual, and salience networks. For the structural connectome of adult MDD, local graph metrics of brain regions comprising the default mode, limbic, or salience networks reflect the severity of mood symptoms and could modulate the influence of environmental factors to mood symptoms. For MDD with later onset age of 50's and 60's, changed values of the local and global graph metrics for the structural connectome are related to the intensity of suicidal ideation and processing speed (Li et al., 2017a)

Fourth, graph-theoretic local network metrics are sensitive to treatment response. Regarding the rs-FCN of adult MDD, response for pharmacotherapy with antidepressants is associated with values of local graph metrics intra-modular connectivity values of default mode network. In addition, response to non-pharmacological treatment for adult MDD is related to the network integrity of the rs-FCN, profile of the inter-modular resting state functional connections, and values of local graph metrics for the regions comprising the ventral attention, salience, and sensorimotor networks in the rs-FCN of MDD. Local centrality values of superior and inferior frontal cortices calculated from the structural connectome of MDD are associated with both treatment-related changes and disease prognosis.

4.2. Current limitations and future directions of graph theory approach for studies of MDD brain

Conventional structural or functional brain connectome only provides information of one-by-one brain inter-regional connectivity strengths. On the other hand, graph metrics provide the distribution of brain inter-regional connectedness, in terms of 1) the balance of integration versus segregation across the whole brain, 2) presence of communities segregated with tighter connectivity among the community members, and 3) profile of core influencing brain regions which are more tightly connected with other regions by way of either white matter tracts or coherent functional oscillations (Rubinov and Sporns, 2010). However, for now, studies that applied graph theory approach for the brain connectome of patients with psychiatric disorders including MDD have several limitations to be addressed.

First, smaller number of studies to derive the graph metrics from the white matter-based structural connectome of MDD have been reported compared to studies for resting-state functional connectome (Ho et al., 2018; Zheng et al., 2019). Further studies that applied graph theory to the brain structural connectome are required. Also, paired comparisons of structural and functional graph metrics within a same study could more characterize the similarities and differences of network organization measured using the graph metrics between structural and functional connectome in MDD (Koubiyr et al., 2019). Second, number of nodes or brain regions comprising the brain connectome could affect the characteristics of graph metrics (Shen et al., 2013). Application of optimal brain parcellation scheme that provides not only the sufficient spatial resolution but also the appropriate number of nodes or brain regions comprising the network are required (Farahani et al., 2019; Ribeiro de Paula et al., 2017). Third, although there are some meta-analytic studies for the global graph metrics (Imms et al., 2019), only a few studies conducted meta-analysis of local graph metrics or community membership (Yun et al., 2020). Local graph metrics of centrality values follow nonparametric distribution (Rubinov and Sporns, 2010). Also, meta-analysis of community membership for brain connectome (Kaiser et al., 2015) needs to integrate the spatial information of community assignment distributed across the whole brain (Crossley et al., 2016; Sporns, 2018). Fourth, few studies for MDD have examined graph metrics for the multi-modal imaging in which structural and functional connectomes are combined as one. Future studies that introduce more reliable pipelines which enable the integration of structural and functional connection into the one matrix (Lee and Xue, 2017; Meunier et al., 2020; Yu et al., 2018; Yu et al., 2016) or as multi-layered format (Mandke et al., 2018) are required. Fifth, further longitudinal follow-up studies that examine the stable or changing patterns of graph metrics for the structural and functional connectomes of MDD patients across the multiple mood episodes and remission status have to be conducted (Ganella et al., 2018; Garcia-Ramos et al., 2017).

4.3. Limitation of current review

The current study has some limitations to be addressed. First, the current review did not apply the meta-analytic approach to combine the study-level results and therefore could not report effect sizes for the differences of graph metrics between MDD versus HC. Rather, the current review was more focused on illustrating the detailed organization of brain structural and functional connectomes in MDD reported in recent key articles. Second, the current review did not explore the relationship between white matter-based structural connectome versus functional connectome [inter-regional distribution of time-varying functional brain activation in resting state] in MDD (Yao et al., 2019). With future studies that explore degrees of synchronization-decoupling between two modalities of structural connectome and functional connectome (Hahn et al., 2019; Neudorf et al., 2020), deeper understanding of MDD pathophysiology reflected in the brain structural-functional connectome interaction might be enabled as already done for corpus callosum agenesis (Yuan et al., 2020), cancer with brain metastasis (Hua et al., 2020), multiple sclerosis with clinically isolated syndrome (Koubiyr et al., 2019), schizophrenia (Zhu et al., 2019), and cannabis users (Kim et al., 2019), among others.

5. Conclusions

To the best of the authors' knowledge, the current review illustrated the most updated (published during the 2015–2020) study findings regarding the structural and functional brain connectome for MDD at multi-layered levels regarding the 1) effects of clinical features for the global network integration versus segregation, 2) attenuated selective intra-modular connection and stronger inter-modular connection, 3) changed distribution of brain inter-regional connections reflected in the differential local graph metrics compared to HC. Further studies that explore the graph metrics-based neural correlates of clinical features, cognitive styles, treatment response and prognosis in MDD are required.

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Author statement

JYY and KYK conceived and designed the study idea. JYY managed literature searches and wrote the manuscript and designed the figure. JYY and KYK critically reviewed the manuscript. All authors contributed to and have approved the final manuscript.

Ethical statement

The authors have no financial and personal relationships with other people or organizations that could inappropriately influence (bias) the current work.

The current work described here has not been published previously (except in the form of an academic thesis), and is not under consideration for publication elsewhere, and is approved by all authors.

Author contribution

JYY and YKK conducted conceptualization, project administration, and review & editing of final draft. JYY conducted resource preparation, investigation, writing of the original draft, and funding acquisition.

Declaration of Competing Interest

The authors declare no conflict of interest.

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