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Review

Neuroimaging features of cognitive impairments in schizophrenia and major depressive disorder

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***Abstract*:** Cognitive dysfunctions are one of the key symptoms of schizophrenia (SZ) and major depressive disorder (MDD), which exist not only during the onset of diseases but also before the onset, even after the remission of psychiatric symptoms. With the development of neuroimaging techniques, these non-invasive approaches provide valuable insights into the underlying pathogenesis of psychiatric disorders and information of cognitive remediation interventions. This review synthesizes existing neuroimaging studies to examine domains of cognitive impairment, particularly processing speed, memory, attention, and executive function in SZ and MDD patients. First, white matter (WM) abnormalities are observed in processing speed deficits in both SZ and MDD, with distinct neuroimaging findings highlighting WM connectivity abnormalities in SZ and WM hyperintensity caused by small vessel disease in MDD. Additionally, the abnormal functions of prefrontal cortex and medial temporal lobe are found in both SZ and MDD patients during various memory tasks, while aberrant amygdala activity potentially contributes to a preference to negative memories in MDD. Furthermore, impaired large-scale networks including frontoparietal network, dorsal attention network, and ventral attention network are related to attention deficits, both in SZ and MDD patients. Finally, abnormal activity and volume of the dorsolateral prefrontal cortex (DLPFC) and abnormal functional connections between the DLPFC and the cerebellum are associated with executive dysfunction in both SZ and MDD. Despite these insights, longitudinal neuroimaging studies are lacking, impeding a comprehensive understanding of cognitive changes and the development of early intervention strategies for SZ and MDD. Addressing this gap is critical for advancing our knowledge and improving patient prognosis.

Keywords: Schizophrenia, Major depressive disorder, Neuroimaging, Processing speed, Memory, Attention, Executive function

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Introduction

Cognitive functions refer to a series of abilities, including attention, executive function, memory, problem-solving skills, reasoning, and directional ability, which play a vital role in our daily life.[1] It is a judgment ability of the brain to reflect to the characteristics, states, and mutual relations of objective things, as well as to reveal the meaning and function of external objects to people. In other words, cognition is akin to high-level mental function.

There is growing evidence that cognitive deficits are recognized as characteristic of schizophrenia (SZ) and major depressive disorder (MDD). The symptoms of SZ are complex and can include psychotic symptoms, sensory perception disturbances, social withdrawal, apathy, and cognitive dysfunction.[2,3] Cognitive deficits in SZ have significant implications for clinical outcomes. Researchers have indicated that cognitive impairment can be detected prior to the onset of clinical symptoms in SZ[4] and even can predict the alleviation of symptoms in patients with SZ.[5] Notably, besides patients with ongoing SZ,[6] cognitive abnormalities have also been seen in the remission of SZ symptoms,[7] even in relatives[8] and

people with high risk factors for this disease.[9] MDD is a common mental disorder, which is characterized by diminished interest and persistent sadness in daily life.[10] Diagnosis of MDD should be based on standard criteria according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), which encompasses symptoms such as a persistently depressed mood, loss of energy, decreased ability to concentrate, inappropriate feeling of guilt, loss or gain of appetite, insomnia, irritability, thought of death, etc.[11] Notably, up to 50% of suicides worldwide occur during an episode of depression, and people with MDD are almost 20 times more likely to commit suicide than the general population.[12] In addition, MDD advances the risk of heart disease, diabetes, cancer, stroke, hypertension, obesity, and Alzheimer's disease (AD).[13] Importantly, given that cognitive dysfunctions are often overlooked during treatment of MDD, there is a long-term disability after remission.[14,15] More recently, studies have shown that cognitive dysfunction in MDD patients is significantly associated with reduced quality of life (QOL), especially mental QOL.[16,17] Although both SZ and MDD can involve cognitive impairments, their typical symptoms are inconsistent. A review indicates that the most impaired cognitive domains in SZ are processing speed, memory, executive function, attention, language, and social cognition,[18] while the significant cognitive deficits in MDD patients are identified for processing speed, attention, memory, and executive function.[19] Notably, there is overlap in certain domains of cognitive impairments in SZ and MDD, including processing speed, memory, attention, and executive function. However, it is unclear whether the underlying mechanisms causing these cognitive impairments are same. In fact, there is limited literature comparing cognitive impairments in SZ and MDD.

In recent years, neuroimaging studies including functional magnetic resonance imaging (fMRI), electroencephalogram (EEG), and positron emission tomography (PET) have revealed changes in mental illness from multiple perspectives and have become valuable diagnostic tools. These non-invasive approaches can help researchers further understand the state of the brain of psychiatric disorder patients by studying the variation of brain structure, function, large-scale brain network, and topological features and provide new ideas for the etiology, assessment, and treatment of cognitive impairment in mental illness.

In this review, we aim to summarize and compare the neuroimaging features of overlapped cognitive impairments in SZ and MDD patients based on literature retrieved from PubMed dating from 1992 to January 2024, involving processing speed, memory, attention, and executive function (Table 1), with hope for providing a new perspective for understanding the mechanism and treatments of these domains of cognitive impairments.

Table 1. Comparison of neuroimaging studies on processing speed, memory, attention, and executive function of SZ and MDD.

	Schizophrenia	Major depression disorder
Processing speed	Widespread disruptions in integrity of WM[20–23]; Disruptions in topological structure of WM[24]	Widespread disruptions in integrity of WM[25,26]; Cerebral small vessel disease[27,28]
Memory	*Working memory* Increased activation of PFC[29–31]; Decreased activation in PFC[32–34]; Stronger FC within the DMN[35,36]; Lower FC within the FPN[37,38]	*Autobiographical memory* Disruptions in network comprising the PFC, MTL, limbic system, and occipital lobe[39]
	Episodic memory Decreased activation of PFC[40–42] and MTL[40,42,43] regions; Lower GMV of MTL[44,45]	

(Continued)

Table 1. (Continued)

	Schizophrenia	Major depression disorder
Attention	Decreased activation PFC activity[46]; Decreased activation of the FPN[47]; Abnormal function of the VAN[48–51]	Lower FC within the FPN[52,53]; Stronger FC within the VAN[54,55]; Decreased nodal degrees of DAN[56]
Executive function	Abnormal FC between the DLPFC and both the SPL and IPL[57]; Decreased activation in the DLPFC, ACC, thalamus[58]; Abnormal FC between DLPFC and cerebellum[59]	Increased activation in DLPFC[60–64]; Increased FC between DLPFC and SMG[65]; Decreased FC between DLPFC and ACC[66]; Abnormal FC between DLPFC and cerebellum[65,67]; Lower fALFF and GMV in hippocampus-amygdala nuclei[68]

ACC, anterior cingulate cortex; DAN, dorsal attention network; DLPFC, dorsolateral prefrontal cortex; DMN, default-mode network; fALFF, fractional amplitude of low-frequency fluctuation; FC, functional connectivity; FPN, frontoparietal network; GMV, gray matter volume; IPL, inferior parietal lobule; MTL, medial temporal lobes; PFC, prefrontal cortex; SMG, supramarginal gyrus; SPL, superior parietal lobule; VAN, ventral attention network; WM, white matter.

Processing speed

Processing speed deficits in schizophrenia. Processing speed is defined as capacity to fulfill rudimentary or intricate tasks that require persistent attention efficiently.[69] As for SZ patients, processing speed is the most severely impaired, which patients' average performance is about 1.5 standard deviations lower than that of healthy controls.[70] The presence of myelinated white matter (WM) facilitates efficient electrical signal transmission, thereby contributing to the overall speed of neural communication in the brain.[71] Fractional anisotropy (FA) is one of the most commonly used indicators to assess the integrity of WM, and it is related to the axon diameter and membrane density of WM fiber bundles. Numerous studies have reported a significant association between the widespread reduction in FA and the declined processing speed in SZ.[20–23] Although there is evidence that WM impairment is present in other cognitive impairments, the decline in FA only mediates processing speed deficits.[20] Dysfunctional processing speed has been confirmed to mediate the deficits in working memory and executive function.[72,73] That is, damage of WM integrity may mediate a decline in processing speed in SZ and further lead to other domains of cognitive dysfunction. Over the past two decades, researchers have consistently suggested that impaired brain connectivity is a key contributor to functional disability in SZ.[3,74] It is hypothesized that disruptions in WM microstructure may contribute to processing speed deficits observed in SZ, possibly through impaired connectivity and information processing within neural networks. The disruption of inter-hemispheric connectivity, evidenced by the alteration of commissural fibers like the anterior commissure,[75] corpus callosum (CC),[76,77] and fornix,[78,79] implies impaired connectivity between the left and right hemispheres of the brain, which may represent a significant factor contributing to the decline in processing speed. The human brain is a complex system, and disruptions in the topological structure of WM can reflect abnormalities in the separation and integration of brain networks of SZ patients.[80] A study, employing first-episode, drug-naïve SZ patients, confirms that characteristic path length of WM network moderates the mediating effect of processing speed to working memory.[24] Notably, abnormal WM structure not only reflects the processing speed of SZ patients, but also can distinguish patients who are resistant to treatment from those who are responsive to treatment.[81,82] The majority of studies investigating WM damage in patients with SZ have relied on diffusion tensor imaging (DTI); however, a recent study indicates that diffusion-weighted imaging appears to provide a more comprehensive understanding of the WM abnormalities associated with processing speed deficits in patients with SZ.[83]

Processing speed deficits in major depression disorder. Processing speed is considered as a core cognitive deficit in MDD patients, as it can mediate other types of cognitive impairments such as memory and executive functions.[27] The intricate connections between WM integrity, processing speed, and MDD have been concerned in several studies. Kieseppä *et al.*[84] investigate the relationship between

WM integrity, processing speed, and depressive symptoms in a sample of older adults. The researchers indicate that reduced WM integrity, specifically in the frontal regions, is associated with slower processing speed in participants with MDD. Shimony *et al.*[25] indicate that FA and mean diffusivity (MD) of CC has correlation with the processing speed of patients with MDD. A large sample size study employing the partial least squares regression reveals more wide abnormalities in WM integrity, including the cingulum bundle, CC, external capsule, inferior longitudinal fasciculus, inferior occipital longitudinal fasciculus, superior longitudinal fasciculus (I–III), superior frontal, and left uncinate fasciculus, which can be regarded as the predictors of reduced processing speed in MDD patients.[26] However, no brain structural changes related to cognitive impairment are found in remitted MDD, suggesting that the disruption of WM integrity in MDD patients is caused by mild cognitive impairments (MCI), and remitted MDD does not contribute to WM changes. While Yeh *et al.*[85] verify elderly patients with MDD still experience processing speed deficits during symptom remission. Age may be an important factor. Of note, although there is widespread WM damage, the most commonly reported regions affected are the frontal lobe and CC in MDD.[25] However, cross-sectional analysis cannot determine whether the remitted MDD group faces a higher risk compared to the MCI group. A longitudinal study is needed to compare the cognitive trajectories of MCI and remitted MDD. Meanwhile, the processing speed of treatment-resistant MDD improves after deep brain stimulation of the subcallosal cingulate WM,[86] indicating that WM even could be seemed as a potential therapeutic target for enhancing processing speed in MDD patients. These findings support the notion that WM abnormalities may mediate the association between MDD and processing speed impairments. Importantly, a large body of literatures suggest white matter hyperintensities (WMH), validated as a marker for cerebral small vessel disease (SVD), are related to declined processing speed in MDD patients. Oberlin *et al.*[27] confirm increased peak width of skeletonize MD, validated as a marker for SVD, predicting poorer processing speed in MDD. They believe that MDD impairs the brain's ability to compensate for microvascular damage. Furthermore, a stronger association is observed between the severity of WMH and limited improvements in processing speed.[28] Other studies also indicate the relationship between vascular burden and processing speed in MDD patients.[87,88] That is, SVD may be a factor leading to processing speed decline in patients with depression. Notably, the possible mechanism of myelin damage is chronic WM ischemia associated with intrinsic cerebrovascular disease.[89] Some studies have advocated classifying some depression as 'vascular depression', a subtype with more pronounced cognitive dysfunction, especially processing speed.[90,91]

Although WM abnormalities related to processing speed have been reported in both SZ and MDD, studies on SZ have mainly focused on WM connectivity abnormalities, while studies on MDD have focused on both WM integrity and WMH associated with SVD. This is consistent with the view that WM is a disorder characterized by impaired brain connectivity integration, while MDD is associated with vascular depression.

In addition to WM damage, numerous studies demonstrate that abnormalities in gray matter (GM) may also be associated with decreased processing speed in these two diseases. A region of interest-based fMRI study discovers significant correlations between processing speed in individuals with SZ and functional connectivities (FC) in several brain regions. Specifically, the study reveals that FC between the precentral gyrus/posterior central gyrus and thalami, as well as between the right cerebellum and thalami, are positively correlated with processing speed in SZ.[92] Clark *et al.*[93] confirm relationship between cerebellum cortex and processing speed of SZ. Nancy Andreasen's cognitive dysmetria theory posits that disrupted connectivity between the prefrontal cortex (PFC), thalamus, and cerebellum may underlie psychosis.[94,95] In addition, FC of left superior frontal gyrus-insula,[96] volume of the hippocampal[97] and regional homogeneity value of left cuneus and right superior occipital gyrus[98] are also considered to relate with processing speed in SZ. Importantly, decreased dynamic FC between the left hippocampus and right middle frontal gyrus also have been verified to the mediator of the relationship between the severity of depressive symptoms and processing speed in MDD. And, volume of the orbitofrontal cortex is confirmed to link with processing speed of both MDD and SZ.[99]

Notably, in contrast to WM structural abnormalities, the results for GM alterations related to processing speed appear inconsistent. Future research could focus on unraveling the underlying mechanisms that link these factors, which may

ultimately guide the development of targeted interventions for improving cognitive outcome.

Memory

Memory deficits in schizophrenia

Working memory. Initially, working memory is conceptualized as 'the temporary storage of information that is being processed in any of a range of cognitive tasks'.[100,101] It is the foundation for the successful execution of complex behaviors, regardless of the cognitive domain involved. The dorsolateral prefrontal cortex (DLPFC) is one of the most widely studied regions in working memory and is modulated by activation of dopamine D1 and D2 receptor.[102–105] Studies manifest drugs releasing dopamine can induce symptoms of SZ in healthy participants, what's more, aggravate symptoms in patients with SZ.[106,107] Anodal stimulation in left DLPFC using 1−2 mA current for 20−30 min is certified to be effective in advancing working memory both in healthy subjects and SZ patients,[108–111] which indirectly verifies the worth of DLPFC in working memory. Neuroimaging studies are applied to interpret the hemodynamics of PFC disorders in working memory in SZ patients, however, with divergence. PFC displays high activation during the working memory paradigm in SZ individuals in some studies, which is given rise to the different cognitive load in working memory tasks.[29–31] Yet, others researches show decreased activation in PFC due to the impaired function of the PFC region.[32–34] Van Snellenberg *et al.*[112] consider this inconsistency principally is relied on working memory task performance.

Notably, deficits in working memory in SZ patients may be not merely associated with the DLPFC. It has been proved that SZ patients have reduced FC in hippocampal-DLPFC[113] and parietal cortex-PFC[34] in working memory task. A PET study provides the evidence that SZ patients have a deficit in releasing dopamine in the DLPFC. More importantly, this deficit also spreads to other cortical and extrastriatal regions including the midbrain. Consistent with many other studies, they also indicate that the capacity of releasing dopamine in DLPFC region is significantly correlated with working memory, suggesting that decreased release of dopamine may affect frontal cortical function.[102] Recent researches extend the effect of dopamine on working memory from a local PFC to a whole-brain network.[114–116] A network control theory framework verifies the capacity to control global reconfigurations of brain states declines in SZ.[117] A lot of large-scale networks studies also confirm that the decline of working memory function in SZ patients is not only limited to PFC. Stronger FC within the default-mode network (DMN),[35,36] as well as hypoconnectivity within the frontoparietal network (FPN)[37,38] and among large-scale networks, involving in the FPN, DMN, cingulo-opercular or salience network (SN)[118,119] have also been certified in a certain of studies exploring the neural mechanism of working memory impairment in SZ.

The role of glutamate in disorder of working memory in SZ patients should not be ignored. Kaminski J *et al.*[120] uncover a positive correlation between working memory-dependent activation and glutamate in unmedicated SZ patients using multimodal imaging. Another study confirms a negative association between frontal glutamate and striatal dopamine in healthy volunteers.[121] Meta-analytic evidence also displays that glutamatergic agents might improve cognitive symptoms in SZ.[122] Moreover, a study reveals that higher dose of roflumilast, a phosphodiesterase-4 (PDE4) inhibitor, leads to decreased activity in the PFC during working memory tasks, specifically in the bilateral DLPFC. The authors consider that this effect is due to PDE4 inhibition, which elevates intracellular cyclic adenosine monophosphate (cAMP) levels in the striatum and frontal cortex. These changes lead to increased dopamine synthesis and turnover in the striatum, as well as enhancement of the dopamine D1 receptor/PKA/DARP-32 signaling cascade in the frontal cortex.[123]

Episodic memory. Episodic memory is a neurocognitive system that enables the conscious recollection of events as they were previously experienced.[124] In the past few decades, neuroscience studies have almost identified PFC and medial temporal lobes (MTL, especially hippocampus) as important regions for maintaining normal episodic memory. The episodic memory task is thought to consist of two parts, encoding and retrieval. Ragland *et al.*,[40] employing Relational and Item-Specific Encoding paradigm, discover decreased DLPFC in SZ during relational *versus* item-specific encoding as well as reduced hippocampus activity during the retrieval success compared to healthy controls. Consistently, numerous studies confirm the decreased activation of PFC[41,42] and MTL[42,43] regions in SZ patients during episodic memory tasks. Moreover,

the reduced volume of hippocampus also has been considered to link with impairments of episodic memory in SZ patients.[44,45] Interestingly, some studies consider that encoding is more impaired than retrieval in SZ patients,[125–127] possibly attribute to deficits in using efficient encoding strategies.[128,129] Research indicates that the use of deep encoding strategy enhances recognition memory in individuals with SZ and leads to a pattern of encoding-related brain activity more closely resembling that observed in control participants by employing fMRI,[130] suggesting that changing the encoding mode is an effective way to improve episodic memory in SZ patients. In light of abnormalities in both the PFC and MTL, it has been suggested that there is a disruption in the frontotemporal network.[131] Dugré *et al.*[132] reveal reduced connectivity between the posterior hippocampus and DMN regions including the precuneus, the supramarginal gyrus, and the ventromedial PFC, but increased posterior hippocampus–intracalcarine cortex connectivity during the retrieval condition. In addition, posterior hippocampus–dorsomedial prefrontal cortex (DMPFC) connectivity decreases during the encoding condition, relative to health participants. A study based on the whole-brain network manifests the integration of SZ during encoding and retrieval tasks is higher in DMN, FPN, and cingulo-opercular network, and the recruitment is higher in dorsal attention network (DAN), visual network (VN), and subcortical network during retrieval task.[133]

A randomized clinical trial (RCT) fMRI study demonstrates that 7.5 mg AQW051, an orally bioavailable α7-nicotinic acetylcholine (nACh) receptors partial agonist, has an effect on hippocampus activation during episodic memory task, especially during encoding task.[134] Kitagawa *et al.*[135] offer the evidence for effect of the α7-nACh receptors partial agonist on health humans during episodic memory task. Moreover, dysregulation of glutamatergic neurotransmission has been implicated in the pathobiology of the SZ, ascribed largely to the hypofunction of the *N*-methyl-d-aspartate (NMDA) receptor. A fMRI study provides evidence for the modulation of the prefrontal and hippocampal activation during episodic memory processes after administration of the Ketamine (a NMDA receptor blockade).[136] Notably, the frontal and hippocampal regions have been certified to contain dense populations of NMDA and nACh receptors.[137,138]

Memory deficits in major depression disorder

Autobiographical memory. Impairment of memory is a significant cognitive issue among individuals with MDD, with autobiographical memory (AM) being frequently highlighted as particularly affected.[139] AM, referring to the recollection of specific experiences and events from one's own life, is a part of long-term declarative memory, which involves in episodic elements and semantic element.[140] The term is closely related, but not identical, to episodic memory, which dependents on a special kind of conscious awareness called autonoetic awareness. That is, while AM encompasses a broader scope of personal memories, including both episodic and semantic information, episodic memory specifically involves the recall of detailed personal experiences and events. Interestingly, in healthy people, the recall of AM tends to be skewed toward positive events.[141] In contrast, MDD patients exhibit a preference to negative memories, potentially contributing to the enduring negative mood observed in this population.[142–144] Some studies indicate that AM disorder not only increases the risk of depression relapse, but also contributes to poor prognosis of MDD patients.[145,146] Hence, AM abnormality is growingly becoming a potential target of MDD treatment and etiology research. A network of brain regions encompassing the PFC, MTL, limbic system, and occipital lobe has been identified in association with AM.[39]

In fact, activity in the PFC is linked to initial semantic processing and the selective, controlled retrieval of stored memories.[147,148] Young *et al.*[149] demonstrate that individuals with depressive symptoms exhibit reduced activity in the DMPFC and increased activity in the DLPFC when retrieving both positive and negative memories. Sperduti *et al.*[150] report similar findings to those mentioned previously. Subsequently, the medial frontal polar cortical activation is confirmed to increase in MDD participants during the specific memories compared to health volunteers.[151]

Other vital regions associated with AM are the hippocampus and parahippocampal gyrus. An fMRI study shows that patients with depressive symptoms have significantly reduced activity in the hippocampus and parahippocampal gyrus when recalling AM memories compared to healthy controls.[143] Hach *et al.*[152] also confirm, in AM recall, reduced connectivity between hippocampus and DMN relative to the control

group, as well as decreased activity in the hippocampus and parahippocampal gyrus. Moreover, some studies indicate reduced volume of hippocampus in MDD patients in AM recall,[153,154] which can also be observed at the high risk of developing MDD groups.[155] The hippocampus and parahippocampal cortex share widespread anatomical and FC,[156] as well as constitute core parts of the AM network.[39]

Amygdala, as a core region of limbic system, serves as the central hub for processing both positive and negative emotions. Young *et al.*[157] manifest that MDD participants display lower activity in left amygdala, also have reduced connectivity with regions of the SN in positive recall of specific memories compared with the control group. Importantly, besides the MDD group, the high-risk and remitted MDD groups show hyperactivity in the left amygdala compared to the control group during the negative recall. The findings suggest that heightened amygdala activation during the recall of negative memories could serve as a trait-like marker of depression. This is supported by the fact that both vulnerable groups exhibit activity levels comparable to those of the depressed group, which are higher than those observed in the control group. A study employing 14 unmedicated remitted depressed patients certifies that bilateral amygdala response during encoding of valenced words predicts increased recall of negative self-referent words following sad mood induction.[158] A separate study reveals the involvement of the amygdala in the retrieval of memories is associated with happy faces among individuals with depression, whereas this involvement is not observed in individuals in remission and health people.[159] A RCT supports an idea that training to enhance the hemodynamic response of positive memories in the amygdala significantly reduces depressive symptoms in MDD patients.[160] In addition, there is an increased amygdala response to hidden happy faces and a decreased amygdala response to hidden sad faces after real-time functional magnetic resonance imaging neurofeedback (rtfMRI-nf),[161] which appears to be similar to the changes seen after treatment with antidepressants.[162] Hence, amygdala rtfMRI-nf, as a non-invasive treatment, has been considered as an efficient method to improve the AM disorder in MDD.[163]

Overall, memory impairment has been extensively reported in both SZ and MDD patients. Notably, SZ patients exhibit a higher likelihood of experiencing impairment of working memory and episodic memory, while MDD patients are more prone to AM abnormalities. Interestingly, despite variations in the types of memory impairment, similar brain regions are implicated, particularly the PFC and the hippocampus. Importantly, aberrant activity in the amygdala appears to be almost exclusively associated with memory disorders in MDD patients, potentially contributing to their heightened susceptibility to mood dysregulation.

Attention

Attention impairments in schizophrenia. Attention is a critical factor in many other cognitive functions, namely, attention deficit may impact on other cognitive function, such as executive function and memory. Impaired attention is a central symptom of SZ, impacting the sustained and selective domains. A widely accepted network, namely FPN, is verified by a number of neuroimaging studies using a series of attention-related tasks.[164–166]

PFC is deemed as a vital region of FPN, and it has been evidenced to be related with attention deficits in SZ patients. Both PFC activity[46] and connectivity with other brain regions[167] are found to be significantly associated with attention deficit in SZ patients. While attention, being a complex cognitive function, involves not only the functions of the PFC but also the parietal lobe and visual cortex.[168] Arkin *et al.*[169] confirm that the early visual cortex is hyperactivated in individuals with SZ during the visual search phase of the task. In addition, disruptions are observed in the connectivity between late visual components, as well as between the PFC and the DAN in SZ. Furthermore, the authors indicate that some individuals with SZ may be able to utilize the attentional control system to compensate for deficits in the visual cortex and PFC. While, abnormal function of the ventral attention network (VAN) is also frequently reported during different selective attention tasks involving attention distracting stimuli, such as visual oddball task,[48] auditory oddball task,[49,50] and visual targets combined with auditory distractors task.[51] DAN and VAN are the core network of 'top-down' attention mechanism,[170] and those findings suggest that disruption of the 'top-down' attention network is a factor contributing to attention deficits in SZ patients. Indeed, the hippocampus also appears to show greater activation during the distraction task.[171] A recent high-density EEG study

conducted by Williams *et al.*[172] also suggests that there is abnormal functioning of the hippocampus and PFC in patients.

In fact, attentional deficits are evident in individuals experiencing their first-episode of SZ, characterized by reduced target detection capabilities and heightened activation of the FPN.[47] Even more, healthy siblings of SZ patients exhibit significant differences during sustained attention task. The study indicates that drug-naïve healthy siblings of individuals with SZ exhibit distinct cortical activation patterns in various frontoparietal regions associated with motor programming, target detection, and cognitive control, despite demonstrating normal behavioral performance. They then identify a specific cortical area, namely the left insula, where the differences between 'at-risk' subjects and normal controls are significant solely under higher attention demand conditions.[173] Sambataro *et al.*[174] also certify that siblings of SZ patients show decreased activation in dorsal anterior cingulate cortex (dACC) during task, along with increased FC with the DLPFC in comparison to healthy controls. Although the regions reported to have abnormalities are not identical, it is certain that: (1) abnormal activity in PFC not only exhibits in SZ patients but also in high-risk group for SZ; (2) in addition to the positive symptoms of SZ, there is a genetic risk for attention deficit.

Notably, there are several studies that report the role of nicotine in restoring attention in SZ patients. Smucny *et al.*[175] suggest nicotine may normalize the deficits on VAN connectivity. Nicotine has also been confirmed to correct the hyperactivity in ventral parietal cortex and hippocampus hyperactivation in attention tasks in SZ patients.[176] A notable characteristic of SZ is the high prevalence of smoking (70% or more[177]) among individuals with the illness. Patients also consume a higher amount of nicotine per cigarette and smoke more cigarettes per day compared to healthy smokers.[178] While patients may smoke for various reasons, a significant contributing factor could be a form of 'self-medication' to correct a deficit in endogenous nicotinic signaling leading to cognitive impairments. In fact, the nACh receptor has been regarded as target to correct cognitive deficits in SZ.[179,180]

Attention impairments in major depression disorder. A typical cognitive disorder in MDD, described as 'diminished ability to think or concentrate', has been considered as one of the diagnostic criterions in MDD.[181] Consistently, Ferrari *et al.*[182] suggest that one of the most common and earliest premonitory symptoms of people with current episodes depression was deficit in attention.

Consistent with attentional deficits in SZ, abnormalities in PFC and FPN function also play a critical role in MDD patients. Some studies confirm that selective attention in MDD patients is related to intrinsic hypoconnectivity of the FPN.[52,53] Dynamic FC in cerebellar-DLPFC is certified to have a positive link with sustained attention of non-first-episode MDD.[183] A VBM study supports an idea that the gray matter volume (GMV) over the inferior frontal gyrus is significantly correlated with sustained attention of unremitted MDD patients.[184] In fact, studies have pointed to differences in brain function and structure in MDD patients with different responses to antidepressant treatment. Li *et al.*[185] indicate that remitted patients exhibit mild visual attention deficits, which are positively correlated with reduced GMV in the left postcentral parietal gyrus and bilateral superior/medial frontal gyrus, in contrast, non-remitting patients display more severe visual attention deficits, linked with GMV reduction in the left precentral parietal gyrus. Importantly, besides the patients with MDD, high-risk MDD group still develops attention deficits. The reduced cortical thickness of right hemisphere not only has relation to attention impairments, but also mediates the association of familial risk with measures of inattention.[186] Furthermore, many large-scale network studies have also elucidated the neural basis of abnormal attention in MDD patients. A subtype study of MDD reveals that hyperconnectivity within the VAN is negatively correlated with sleep maintenance insomnia in insomnia-dominated subtype of MDD, which implies the overactivation of the attention network may be an important factor leading to sleep disorders in MDD patients.[54] It is consistent with another research that hyperactivity in the VAN is linked with an overarousal state and insomnia in MDD individuals.[55] A study has found that the nodal degrees of DAN in MDD patients is reduced, which may suggest less efficient in the top-down attention process.[56] Moreover, DAN is thought to antagonize the function of DMN. A rest-meta-MDD study including 1300 MDD patients and 1128 health volunteers observes decreased between-network FC in DAN, sensorimotor network, and VN,

which may be regarded as the neural basis for the universal influences of psychomotor retardation on attentional processes.[187]

Moreover, baseline hypoconnectivity between the DMN, FPN, VAN, and DAN for non-remitters can distinguish them from controls and increase following antidepressant treatment. In contrast, the intrinsic connectivity in symptom remitters is higher than that in the control group, both at baseline and after remission.[188] This is consistent with the point that MDD patients with different responses to antidepressants have different degrees of visual attention impairment and brain functional and structural changes.[185] Thus, attention-related networks may also be used to predict antidepressant response in MDD patients. Furthermore, the transcranial magnetic stimulation targeting the PFC can improve sustained attention of depressed individuals.[189] And, cognitive-behavioral therapy exhibits distinct advantages over antidepressant medication in ameliorating attention deficits among individuals with MDD, given the increase in FC strength observed between networks responsible for cognitive control and attention.[190]

Executive function

Executive dysfunction in schizophrenia. Research indicates that individuals with SZ exhibit symptoms characteristic of a 'dysexecutive syndrome'. Irrespective of the specific executive task assessed, this patient group displays pervasive impairments in executive functions relative to healthy controls,[191] resulting in impairment in integrating multiple information and processes effectively to complete a target. Indeed, DLPFC plays an important role in executive function in SZ. Sarpal *et al.*[57] indicate that the group of individuals experiencing their first episode of SZ exhibits significantly reduced resting-state FC between the DLPFC and both the bilateral superior parietal lobule and the left inferior parietal lobule, in comparison to healthy individuals. A comprehensive meta-analysis of 41 functional neuroimaging studies employing executive function tasks – such as the delayed match-to-sample, N-back, AX-CPT, and Stroop tasks – reveals that patients with SZ exhibit aberrant activity and deficits in the DLPFC, anterior cingulate cortex (ACC), and the mediodorsal nucleus of the thalamus. Concurrently, heightened activity in other PFC regions suggests a potential compensatory mechanism.[58] In addition to the activity of DLPFC and its FC with other brain regions, the volume of DLPFC is also related to impaired executive function in SZ.[192] Notably, besides the executive dysfunction, the DLPFC also plays a role in attention and working memory deficits among patients with SZ. In fact, executive functioning involves cognition processes that require top-down control to execute goal-directed behaviors, including attention, working memory, cognitive control, lexical generation, response selection, and inhibition. Also, the strength of connectivity of FPN to cerebellar network has been considered to be related with executive function of not only SZ but also their siblings.[59] A meta-analysis reveals that the relatives of SZ exhibit both hypoactivity and hyperactivity in right middle frontal regions that statistically overlapped.[193] In other words, executive dysfunction in SZ may have genetic features. The executive function impairment in SZ may have hereditary characteristics, which can be manifested through brain activity and FC. However, it is currently unclear whether these characteristics can predict the progression to SZ in high-risk individuals. Future research could focus on the neuroimaging features that predict high risk for SZ, in order to develop early non-invasive detection methods and provide opportunities for early intervention in high-risk populations.

Research considers that impairments in network activation, connectivity, and interactions may be associated with disruptions in glutamatergic signaling that have been implicated in SZ, particularly through the activity of the NMDA receptor.[194] It has been proven in animal models that NMDA receptor agonists can improve executive function in SZ.[195] Moreover, cognitive remediation therapy (CRT) also can improve the executive function of SZ. For example, increased activation in left DLPFC, bilateral frontopolar, and ACC is found after 7 week/14 sessions CRT.[196] Another study verifies 2 years/60 sessions CRT increased activation in right DLPFC, reduced connectivity between right DLPFC, ACC and orbital PFC, and increased connectivity between bilateral DLPFC and posterior cingulate cortex during executive function task.[196]

Executive dysfunction in major depression disorder. There is growing evidence supporting that MDD is associated with abnormality of executive function in both younger and older adults.[197,198] Importantly, executive function is confirmed to be the most severely affected cognitive domains[199] and an available predictor for therapeutic effect of

MDD.[200] The abnormal function of the PFC should not be neglected. Increased FC between the right DLPFC and right supramarginal gyrus (SMG) is found when remitted MDD patients experienced multiple executive function tests.[65] SMG is a pivotal component of temporoparietal junction, involving in language, memory, attention, and social processing.[201] That is, enhanced FC may imply a compensatory effect of executive function network. Wang *et al.*[65] further discover increased FC between the right cerebellar Crus I and left DLPFC in patients with MDD. Notably, the cerebellum is thought to be closely related to working memory.[202] Additionally, Liu *et al.*[67] manifest disrupted correlation of FC between the right anterior PFC and the left cerebellum, and interference effect of accuracy during the Stroop test that is considered to estimate execution function in the MDD patients, particularly inhibition.[203] They also verify the frontal and cerebellar regions is strongly associated with impaired executive function in MDD patients.[67] Decreased FC between the dACC and the DLPFC is found in children with greater executive function impairment.[66] Higher activity in dACC is considered needed for greater cognitive control, which is supported by the DLPFC and the FPN. Accordingly, reduced FC between dACC and DLPFC may indicate a breakdown in the ability to communicate between networks in a way that effectively enhances executive function. In addition to abnormal FC between the PFC and different regions, activation and GMV are also associated with impaired executive function in MDD patients. MDD patients show significantly more activation in DLPFC during the N-back task.[60–64]

Abnormalities in hippocampus have also been implicated in executive dysfunction in MDD patients. Poorer executive function is confirmed to be in relation with lower fractional amplitude of low-frequency fluctuation and GMV in hippocampus-amygdala nuclei in MDD individuals.[68] Notably, the hippocampus and amygdala are core regions of the limbic system with extensive connections to the frontal cortex. A study indicates that after short-term administration of vortioxetine, a medication designed to improve executive functions in patients with MDD, there is a reduction in hippocampal activity during the performance of the N-back task in MDD patients.[204] A multiscale neural modeling research reveals increased effective connectivity of PFC to hippocampus in the MDD patients, which may lead to low hippocampal activity.[205] In other words, it is possible that the limbic system contributes to executive dysfunction in MDD patients through its connectivity with frontal regions.

Relation between cognitive impairments and disease progression

Patients with SZ exhibit early-stage deficits in processing speed,[78] memory,[98] attention,[47] and executive function[58] which can be observed even in individuals experiencing their first episode of illness. A study indicates that changes manifest even earlier, providing evidence that some unaffected first-degree relatives exhibit a profile resembling that of patient.[173] Furthermore, those who eventually develop psychosis may demonstrate greater impairment in visual and verbal memory as well as spatial working memory at baseline.[206] Another multiperiod follow-up study over 20 years shows that SZ has mild to moderate developmental impairments in processing speed at the time of the first psychotic episode and relative cognitive immobility thereafter.[207] The trajectory of cognitive function in older patients with SZ was assessed in a comprehensive longitudinal study. The assessment primarily targets adults aged 55 or older who have been diagnosed with SZ around 25 years ago. Notably, a distinctive feature of this sample is the absence of antipsychotic medication during the onset of their SZ, leading to untreated psychosis due to limited therapeutic options. A finding reveals a decline in cognitive function among patients with SZ, with a three-point-per-decade difference observed in Mini-Mental State Examination performance across the entire sample.[208] In fact, there are several studies on the longitudinal study of cognitive impairment in patients with SZ, however, a few is related to neuroimaging. In a longitudinal study involving adolescents with cognitive impairment, the researchers discover that individuals exhibiting pronounced schizotypal features display GM reductions in the left MTL over time.[209] In a recent study utilizing four independent datasets, the MTL is identified as a potential focal point for volume loss throughout all stages of illness in SZ. Additionally, the study demonstrates a sequential progression of dynamic GMV loss epicenters, shifting from posterior to anterior regions. Those findings suggest an increasing pathological burden within the temporal and prefrontal systems as the illness advances.[210] Imaging changes may reflect the neurocognitive profile, characterized by initial frontal and temporal alterations preceding the onset of illness, as

well as subsequent widespread impairments that develop over the course of the disease.

For MDD, cognitive deficits are also present in both high-risk group[211] and first episode of patients.[212] However, more studies tend to elaborate on relationship between progression of MDD and dementia. MDD is considered as a risk factor for dementia.[213,214] A study indicates that, at baseline, nondemented older adults who are acutely depressed and later developed dementia during the study period demonstrate significantly lower cognitive performance compared to acutely depressed individuals who maintain normal cognitive function.[215] A controlled study has shown that although MDD and AD have similar performance in terms of cognitive impairment, AD displays worse cognitive performance and more severe MTL atrophy.[216]

Studying the cognitive trajectories of patients with SZ and MDD is necessary to help understand the effectiveness of interventions. Meanwhile, relevant longitudinal neuroimaging studies are helpful to explore the neural mechanisms of cognitive impairment and guide treatment.

Conclusion

A growing body of literature has focused on cognitive impairment in SZ and MDD, and neuroimaging approaches can provide new perspectives not only to understand the pathogenesis, but also to guide the cognitive remediation. The most impaired cognitive domains in SZ are processing speed, memory, executive function, attention, language, and social cognition while the significant cognitive deficits in MDD patients are identified for processing speed, attention, memory, and executive function. This review aims to synthesize existing neuroimaging studies to discuss several overlapped domains of cognitive impairment, that is, processing speed, memory, attention, and executive function, and compare the corresponding neuroimaging findings in SZ and MDD.

WM abnormalities seem to be related with deficits in processing speed in both SZ and MDD patients. Of note, SZ studies have mainly focused on WM connectivity abnormalities, while MDD studies have concentrated on WMH caused by SVD. This is consistent with the view that SZ is a disorder characterized by impaired brain connectivity integration, whereas MDD is associated with vascular depression. In terms of memory domains, individuals with SZ are more likely to experience impairments in working memory and episodic memory, whereas patients with MDD are more susceptible to abnormalities in AM. Interestingly, despite variations in the types of memory impairment, similar brain regions are implicated, particularly the PFC and MTL. However, aberrant activity in the amygdala appears to be almost exclusively associated with memory disorders in MDD patients, potentially contributing to their heightened susceptibility to mood dysregulation. Then, attention is similarly impaired in SZ and MDD patients, which PFC plays a critical role. Moreover, a range of networks that maintain attention are impaired in both types of patients, involving in FPN, DAN, and VAN. Finally, in executive dysfunction, the activity, FC, and volume of DLPFC play a core role in both SZ and MDD patients.

Importantly, cognitive impairments in patients with SZ and MDD occur very early, not only in patients with a first episode, but also in first-degree relatives at high risk for the disease. Corresponding neuroimaging changes are also seen in these populations. Nevertheless, there is still a lack of longitudinal neuroimaging studies. These studies are essential for comprehending the cognitive changes in patients with SZ and MDD from a broader perspective and for informing early intervention strategies.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Yu-Ting Li: Conceptualization; Writing – original draft; Writing – review & editing.

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Yu-Xuan Shang: Investigation; Writing – review & editing.

Zhu-Hong Chen: Investigation; Writing – review & editing.

Guang-Bin Cui: Supervision; Writing – review & editing.

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