Neuropsychological Trends

37
April 2025

Schizophrenia: a mini review of cognitive function study in multi-modalities of neuroimaging and neuropsychology tests

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DOI: https://doi.org/10.7358/neur-2025-037-alis asatiyah@unimas.my

ABSTRACT

Schizophrenia is a neuropsychiatric disorder that causes people to hallucinate and have unusual or distorted thoughts. Schizophrenia is primarily diagnosed based on symptoms such as hallucination, delusion, abnormal thought disorder, disorganized speech, bizarre behavior, and cognitive impairment. One of the major current discussions in schizophrenia is the poor cognitive function, which includes impairment of attention and working memory. Any abnormality in these sets of cognitive functions limits one's ability to organize daily life, including social life, career, and thought. So far, many studies have been conducted revealing the neural processing of schizophrenia patients. However, very few papers discuss the states of neurocognitive processing from the combinations of multiple modalities of neuroimaging, electrophysiological, and neuropsychological sides in one single article. This review article will discuss previous studies on cognitive function in schizophrenia patients from a neuroscience standpoint.

Keywords: schizophrenia; cognitive function; neuroscience perspective

1. Introduction

Schizophrenia is one of the most common psychiatric disorders in Malaysia, with the government hospital reporting about 2000 new cases each year, indicating an increase in the number of patients with mental disabilities (Free Malaysia Today, 2017). Cognitive function in individuals with schizophrenia is often linked to frontal lobe dysfunction, given the frontal lobe's role in executive functions and cognition (Dixon et al., 2022; Orellana & Slachevsky, 2013; Salgado-Pineda et al., 2007). However, perspectives on the localization of cognitive abnormalities vary. Some studies report no significant impact of frontal lobe dysfunction on cognitive deficits, while others present contrasting evidence (Kaur et al., 2020). Despite the differences, it is a certain fact that any impairment in cognitive function reduces a person's ability to live as a normal, healthy person, as they may not be able to pay attention, have poor memory, poor organizing skills, and be easily distracted (Trivedi, 2006). In neuroscience, neuronal processing is crucially studied using multiple types of neuroimaging techniques in order to investigate the state of cognition. A previous study showed that schizophrenia had diminished N100 and P300 amplitudes, which are significant for attention Brecher et al., 1987. Additionally, another study on Magnetic Resonance Imaging (MRI) in schizophrenia found abnormalities in the structural functions of the ventricles, thalamus, frontal lobe, and basal ganglia (Gilbert & Keshavan, 2001).

In this review paper, multiple types of neuroimaging techniques and electrophysiology tests were discussed in further detail. These tests are Event-Related Potential (ERP), functional Magnetic Resonance Imaging (fMRI), structural Magnetic Resonance Imaging (sMRI), and Diffusion Tensor Imaging (DTI) in revealing the connectivity in brain regions. Furthermore, neuropsychological tests in schizophrenics are being discussed in order to demonstrate the translation of behavioral output in those affected patients.

2. Methodology

This study employs broad keywords to search for relevant literature. The keywords used include “Schizophrenia”, “Schizophrenia AND EEG”, “Schizophrenia AND Event-Related Potential”, “Schizophrenia AND Neuroimaging”, and “Schizophrenia AND Neuropsychological Tests”. The literature was searched using various databases, including Google Scholar, Scopus, and PubMed. The inclusion criteria focused on studies and information related to schizophrenia, particularly in the context of multi-modal

neuroimaging and neuropsychological tests. No specific time frame was set for the literature, as this mini-review aims to provide a comprehensive overview of cognitive functions in schizophrenia without restricting the scope to a particular period.

3. Event-Related Potential

Event-Related Potential is an electrophysiological test that captures neuronal activity through a scalp electrode in response to a stimulus (i.e., auditory, visual, and somatosensory) by time-locking the neuronal electrical response to stimulus onset. There are five main target components of ERP related to cognitive function that are commonly studied in schizophrenia, namely P300, N100, N200, N400, and Mismatch Negativity (MMN).

3.1 N100

N100 is primarily exogenous because it is influenced by the physical characteristics of the stimulus. For example, a study found that N100 amplitudes were reduced in auditory stimulation but not in visual stimulation (Duncan, 1988). N100 also elicits when the stimulus is being attended, as it signifies pre-attentional ability. Schizophrenia patients, who mainly have low attention ability, may display a poor ability to attend to the stimulus given, which explains the smaller amplitude of N100 among them (Squires-Wheeler et al., 1993; Sur & Sinha, 2009).

3.2 N200

N200, also known as N2, is not as widely studied as other ERP components, such as P300. This is because N2 is modality-specific and is evoked by oddball paradigm stimuli, which are either visual or auditory. N2 latencies range from 180 to 325 milliseconds. P300, on the other hand, is more related to subjective probability and may depend on cognitive function and the stimulus. Hoffman et al., (1990) found that the N2 response is elicited before any attention is elicited. This means that it signifies the identification and distinction of stimuli. Brecher et al. (1987) conducted a study on 14 schizophrenic patients and found that the N2 component in these patients was within normal amplitude, but the latency was prolonged. This indicates that there was a delayed N2 response to the stimulus. The delayed response suggests that schizophrenic subjects have a slower reaction time to stimuli than control subjects.

3.3 Mismatch Negativity (MMN)

MMN is a negative deflection component that occurs around 100 to 125 milliseconds after an auditory stimulus. Previous research has shown that MMN is sensitive to changes in auditory stimulation, such as changes in pitch, intensity, location, and tone sequences. MMN is one of the three subtypes of N2. MMN is used to assess auditory sensitivity in people with schizophrenia. Studies found that people with schizophrenia have a smaller amplitude of MMN and an abnormal topographical distribution of MMN (Erickson et al., 2016; Light & Braff, 2005). However, there is some debate about whether MMN findings change over the course of schizophrenia (i.e., from early onset to chronic schizophrenia) (Salisbury et al., 2002).

A recent meta-analysis of MMN in chronic and early-onset schizophrenia found that MMN to deviant stimuli was smaller in chronic schizophrenia patients than in healthy control adults (Cohen's $d > 1.0$) (Haigh et al., 2017). This suggests that MMN could be used as a biomarker for schizophrenia. In that study, 14 healthy adults and early-onset schizophrenia patients (first 12 months of episodes) were studied using two different types of stimuli: pitch deviant and duration deviant. They found that there was no reduction in MMN in first-episode patients to pitch-deviants (Cohen's $d = 0.04$), but there was a small-to-medium reduction to duration-deviants (Cohen's $d = 0.47$). This suggests that pitch deviance may not be a good biomarker for schizophrenia, but duration deviance may be more useful. Another study found that pitch-deviant MMN in chronic schizophrenia patients did not decrease during first hospitalization (Salisbury et al., 2002). This suggests that there is no obvious deficit in sensory or echoic memory functions in early-stage schizophrenia that would explain the reduced MMN amplitude. They predict that MMN amplitude will worsen throughout the course of schizophrenia, but this needs to be confirmed by longitudinal studies.

3.4 P300

The P300 event-related potential component is a prominent electrophysiological marker for schizophrenia. It signifies the attentional ability towards stimuli, and it is the most prominent ERP component being discussed in literature reviews compared to other components. Sun et al., (2005) discovered that the amplitude of P300 among schizophrenics was small compared to the normal group. The P300 latency was negatively correlated with the performance IQ and verbal test, while the amplitude was positively correlated with verbal IQ and total IQ. In short, the study suggested that verbal and total IQ are closely related to P300 amplitude instead of latency (Sun et al., 2005). Some studies

have been done on the comparison of P300 amplitude between schizophrenics with negative and positive symptoms. Positive symptoms describe symptoms such as hallucinations, delusions, and agitated body movement, while negative symptoms include depression, social deprivation, lack of motivation, and poor cognitive function. Liu et al. (2004) categorized schizophrenic patients into two groups based on types of symptoms, whether positive or negative, using the Positive and Negative Syndrome Scale (PANSS). Their results showed prolonged latency and a small amplitude of P300 among negative symptom groups compared to positive groups. Other than that, those with negative symptoms also had prolonged latency in the P200 and N200 ERP components. They claimed that all groups showed a trend of reduced latency in P300, but the most significant reduction was found in schizophrenics with negative symptoms.

Brecher et al. (1987) studied the ERP component among schizophrenic patients and control subjects by using three visual stimuli: a vertical line, a horizontal line (an easy target), and a 3° deviated line (a difficult target). It was clearly seen that P300 amplitude was reduced among schizophrenic patients when difficult targets were compared to easy targets. Meanwhile, the amplitude among control subjects was larger for easy targets and slightly smaller for difficult targets. These findings suggested that schizophrenic patients were not able to respond to the increased demand for processing information.

The use of somatosensory input in triggering P300 was done by Josiassen et al. (1981), and they noticed that P300 amplitudes were smaller than in healthy normal subjects. Another finding was by Duncan (1988), who stated that there were two different interpretations of P300 amplitude based on the stimulus used, whether visual or auditory. Reduced P300 amplitude while using visual stimulation may indicate a schizophrenia state condition, while in auditory stimulation, any reduction in amplitude suggests a possible trait of schizophrenia running in the family (Duncan, 1988; Squires-Wheeler et al., 1993). However, Squires-Wheeler et al. (1993) were unable to find any significant association between P300 amplitude and a familial trait. The P300 component can be divided into two types: P3a and P3b. These two components are generated in different neural loci. P3a originates from stimulus-driven frontal attention mechanisms during task processing, while P3b originates from temporal-parietal activity associated with attention and appears to be related to subsequent memory processing (Polich, 2007). In relation to the differences between these two components in terms of localization and stimulus processing, Bachiller et al. (2015) studied P3a and P3b in 31 schizophrenics using an auditory oddball paradigm to discover the neural generators underlying the cognitive process in schizophrenia. The researchers discovered that there was lower P3b activity in bilateral frontal and cingulate structures among people with schizophrenia. Additionally, less

widespread P3a generator activity was observed in the right medial and middle frontal gyrus compared to the control healthy group (Bachiller et al., 2015).

3.5 N400

This ERP component is used to describe semantic incongruity processing. It is related to the expectancy of a given word to end a sentence. For example, if a sentence is “I went to school by bus”, and we change “bus” to something that is unexpected, such as "tree", the sentence would be ridiculously nonsense, thus elevating the N400 ERP response. The latency of the wave outcome would be around 300 to 600 milliseconds after the stimulus is presented. The N400 component is rarely discussed in cognitive evaluations of schizophrenia, as most of the focus is on more prominent ERP components such as P300 and N100. However, the N400 can be used to study the disordered thinking of schizophrenia. Zhang et al. (1993) studied the N400 in 19 schizophrenic patients and a control group. They found that there was a higher amplitude of N400 when incongruent sentence stimuli were presented. However, the amplitude among schizophrenic patients was smaller when congruent sentence stimuli were presented compared to incongruent sentence stimuli. These results may suggest an impairment of linguistic information processing in schizophrenia.

4. Magnetic Resonance Imaging

Previous studies have shown that schizophrenia patients have abnormalities in brain structures, such as enlarged lateral ventricles (Lieberman et al., 2001), and reduced temporal lobes (Kaur et al., 2020). A study compared the volumes of the temporal and frontal lobes in schizophrenia patients and their siblings. They found that the patients had reduced volumes compared to their healthy siblings (Staal et al., 2000). As more studies are conducted, few other research has indicated that asymmetry in the frontal lobe and temporal areas is associated with early-onset schizophrenia (Fukuzako et al., 1997; Maher et al., 1998).

In a review article, Gilbert and Keshavan (2001) discussed MRI abnormal findings in the ventricles, basal ganglia, thalamus, frontal lobe, temporal lobe, cerebellum, and corpus callosum. As previously mentioned, enlarged ventricles are one of the main abnormalities observed in schizophrenia. However, the ability to clinically diagnose schizophrenia based on enlarged ventricles is not reliable, as this finding is also observed in other disorders, such as Huntington’s disease, Alzheimer’s Disease, and hydrocephalus (Gilbert & Keshavan, 2001). Further discussion of MRI research findings will be presented below.

4.1 Structural Magnetic Resonance Imaging

The advancement of current neurotechnological devices has helped in detecting and exploring the parts of the brain that are associated with the pathophysiology of schizophrenic patients. The use of structural MRI has come a long way in identifying the region of the brain that is linked to schizophrenia. In this paper, we focused on the parts of the brain that are most commonly associated with and studied in schizophrenia.

4.1.1 Temporal lobe

One of the regions in the brain that is most commonly related to schizophrenia is the temporal lobe. The temporal lobe has always been the main focus of investigation due to the notion that it is responsible for auditory and language-related processes and their close relation to thought processing (Koutsouleris et al., 2008). Hence, abnormalities in the temporal lobe are strongly associated with schizophrenia, as this disorder can cause delusions and auditory hallucinations in patients.

In a review article by Shenton et al. (2001), they reported that more than half of the studies found reductions in volume of the whole temporal lobe for schizophrenic patients compared to normal patients. In addition, the part of the temporal lobe that is most being investigated in schizophrenia is the superior temporal gyrus (STG). The disruption of the STG can compromise the integration of language, memory, and cognitive processes because of its role in language production and perception. This disruption may lead to positive symptoms in schizophrenic patients, such as thought disorder and auditory hallucinations (Brent et al., 2016).

Compared to healthy subjects, schizophrenic patients, even those with early onset, showed significantly lower gray matter volume in the left middle and superior temporal gyrus (Tang et al., 2012). A recent study found that patients with reduced gray matter volume in the STG, particularly at the left posterior part, showed an increase in positive symptoms of hallucinations (Nestor et al., 2017). These findings are consistent with previous studies that evaluated only STG gray matter volume and found a reduction in STG gray matter volume in schizophrenic patients (Shenton et al., 2001). In fact, two of the first MRI studies done on the STG also reported a left STG volume reduction. In addition to the STG, the middle temporal gyrus also showed reduced gray matter in early-onset schizophrenic patients compared to healthy subjects (Tang et al., 2012).

Furthermore, schizophrenic patients with a history of serious violence also showed significantly decreased gray matter volumes in the right inferior

temporal gyrus, which extended to the middle temporal gyrus, temporal lobe, and fusiform gyrus, compared to patients who did not have any violence history (Kuroki et al., 2017). According to Nestor et al. (2017), patients with lower gray matter volume of the left posterior fusiform gyrus were associated with both reduced openness and more severe social anhedonia. High levels of social anhedonia mean that the person is not interested in social interactions, and this personality trait has a strong connection to the development of schizophrenia (Germine et al., 2011). The fusiform gyrus, which is located at the inferotemporal cortex, is also proposed to be involved in the recognition of emotional stimuli, operating together with the amygdala (Kuroki et al., 2017). Therefore, the reduced volume of the fusiform gyrus may cause the patient to have less emotion and empathy toward others, thus contributing to the violent behavior of some schizophrenic patients.

4.1.2 Subcortical structures

Subcortical structures, which include the basal ganglia and parts of the limbic system, have also become a significant focus in schizophrenia research. This is because these structures play an integral role in learning and memory, and thus involve higher-order executive functions through their connectivity both structurally and functionally with prefrontal cortices (Okada et al., 2016).

Previous studies found that basal ganglia structures, which include the caudate, putamen, and nucleus accumbens, had larger gray matter volume in schizophrenic patients (Shenton et al., 2001). Recent findings found agreement with the previous studies that reported larger gray matter volumes in the bilateral caudate, putamen, pallidum, and lateral ventricles in schizophrenic patients compared to healthy subjects (Okada et al., 2016). However, they reported a smaller nucleus accumbens, which is in contrast to the previous studies. This could be due to the effect of the medications that the patients consumed, which may interfere with the structural changes, and also the differences in the method of analysis (Shenton et al., 2001).

Schizophrenic patients with larger left lateral ventricular volumes had reduced motor speed, and increased bilateral putamen volumes had decreased executive functioning, working memory performance, and verbal learning (Hartberg et al., 2011). The increase in volume of lateral ventricles, particularly the left lateral ventricles, was the most robust and consistent finding in schizophrenia research (Hartberg et al., 2011; Shenton et al., 2001).

A meta-analysis done by Pedraza et al. (2004), which focused on the published studies from 1990 until 2000, revealed that both the hippocampus and the amygdala had increased volume, particularly on the right side for healthy subjects. Hence, both the hippocampus and the amygdala have

rightward asymmetry, with the right side being much larger than the left side. The hippocampus's role is more towards memory processing, while the amygdala is emotional processing. One study reported that healthy subjects and their siblings also showed rightward asymmetry in the hippocampus and amygdala. Whereas, schizophrenia patients and their siblings showed disruption of the rightward asymmetry pattern with an exaggerated reduction of hippocampus and amygdala volume (Qiu et al., 2009). Other studies also found reduced hippocampus and amygdala, which are parts of the limbic system, in schizophrenic patients compared to healthy subjects (Shepherd et al., 2012; van Erp et al., 2016).

The thalamus, which is also part of the limbic system, is a major relay station in the brain that controls input from many cortical areas and revealed decreased volume in schizophrenic patients compared to healthy subjects (Okada et al., 2016; van Erp et al., 2016). Meta-analysis done by Shepherd et al. (2012) revealed that most studies on schizophrenia showed bilateral thalamic reduction. Qiu et al. (2009) reported decreased thalamus volume, particularly on the right side, in both schizophrenic patients and their close siblings, while other studies reported left thalamic reduction in schizophrenic patients when compared to healthy subjects (Hartberg et al., 2011; Rimol et al., 2010).

4.1.3 Frontal lobe

The frontal lobe and its components have been extensively researched for structural changes, and these changes have been documented in several reviews. Meta-analyses have reported evidence of a bilateral reduction in frontal lobe total volume (Davidson & Heinrichs, 2003; Shepherd et al., 2012; Wright et al., 2000). Regions of significantly reduced gray matter volume were primarily observed in bilateral medial and middle gyri, but also less commonly in inferior, superior, and inferior-medial frontal regions (Shepherd et al., 2012).

Prefrontal cortex volumes were found to be significantly higher in healthy subjects compared to two groups of schizophrenic patients, violent and non-violent (Kumari et al., 2009). Prefrontal cortex sub-regions, such as the orbitofrontal cortex, were found to be reduced in gray matter volume, and this reduction correlated significantly with the impulsivity score in schizophrenic patients. Impulsivity is one of the mediating factors between PFC reductions and the violent and antisocial behavior found in schizophrenic patients (Kumari et al., 2009).

5. Functional magnetic resonance imaging

Functional magnetic resonance imaging focuses on the physiology and activity of the brain rather than its structure. Its principle is based on the blood oxygenation level, where an increase in the Blood Oxygenation Level-Dependent (BOLD) signal means an increase in brain activity.

In schizophrenia research, the connectivity between parts of the brain is being widely investigated, and the default mode network (DMN) is the brain network that is most researched. This is because many parts of the brain, such as the prefrontal cortex which is known to be abnormal in schizophrenic patients, are also coincident with DMN regions. Hence, it is crucial to investigate the role of DMN in schizophrenia to uncover the pathogenesis of the disease.

5.1 Default Mode Network

The default mode network is a network of interconnected brain regions that are active during the resting state, when the brain is not actively involved in any tasks. The DMN includes the medial prefrontal cortex, anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), precuneus, inferior parietal lobule, and parahippocampal gyrus. The term "default mode network" was first coined by Raichle et al. (2001) to reflect the fact that the DMN is thought to be active when the brain is in a "default" state, meaning that it is not actively engaged in any specific task. However, the DMN is also activated during self-monitoring and introspection. Despite the notion that the brain is in a "resting state" when not involved in any task, the energy that the brain uses during rest for neural communication is more than half (60-80%) of what it uses during task conditions, which is only 0.5%-1% (Raichle et al., 2001). This comparison shows that inherent function during rest is as important as task-dependent activity in knowing and understanding the functional characteristics of the brain. This is why research on the DMN in schizophrenic patients is an interesting topic. Parts of the DMN regions are also parts of the brain that have shown abnormalities in structural MRI. Thus, it is hoped that further understanding of the DMN may shed some light on the pathogenesis of schizophrenia.

In schizophrenic patients, the DMN has been shown to have both increased and decreased functional connectivity (Anticevic et al., 2015; Bluhm et al., 2007; Woodward et al., 2011). For example, one study reported decreased functional connectivity between the PCC and other DMN regions such as the MPFC (Bluhm et al., 2007). However, other studies have shown increased functional connectivity in the DMN in schizophrenic patients (Anticevic et al., 2015; Guo et al., 2017; Woodward et al., 2011). The inconsistency in these findings could be due to various factors, such as

heterogeneity of the sample, methods of analysis, sample size, scanners, illness duration, and medication effects (Guo et al., 2017).

Recent research has found that unmedicated and drug-naive schizophrenic patients have increased functional connectivity to the regions in the default mode network, particularly at the prefrontal cortex (Anticevic et al., 2015; Guo et al., 2017; Guo et al., 2015). Schizophrenia is highly heritable, so unaffected siblings of schizophrenic patients, who share similar genetic and environmental backgrounds, also showed increased functional connectivity within the DMN regions when compared with healthy controls (Guo et al., 2017; Guo et al., 2015; Whitfield-Gabrieli et al., 2009). The increase in connectivity (hyperconnectivity) within the DMN in schizophrenic patients may cause disturbances of thought and increase the symptoms of the disease. The disturbances of the DMN in the relatives of the patients further justify the genetic basis of the disease (Galindo et al., 2018).

As discussed earlier in the structural MRI part, the frontal lobe, particularly the PFC, had shown decreased cortical thickness in schizophrenic patients. This finding was consistent with the functional abnormality found at the prefrontal cortex part in the DMN regions of the patients as compared with the healthy subjects. The increased connectivity within the DMN in schizophrenic patients suggests that the patients may be unable to perceive external stimuli, thus impairing performance on attentional tasks. In addition, being unable to suppress the DMN would increase mind-wandering, thus distorting the normal boundary between internal thoughts and external perceptions (Whitfield-Gabrieli et al., 2009).

6. Diffusion Tensor Imaging in schizophrenic

Brain connectivity is the study of the structural communication between brain regions. It has been widely used to investigate the functional and anatomical strength of brain connections. The abnormality findings in structural and functional studies support the hypothesis of abnormal brain function in schizophrenics (Karlsgodt et al., 2010). However, additional support from connectivity studies may strengthen the theories of brain impairment in schizophrenics. A few studies have revealed that the brain region connectivity among schizophrenics differs from the healthy group, especially in tasks related to cognitive function (Orban et al., 2017), and cognitive workload (Godwin et al., 2017). Diffusion Tensor Imaging is an MRI technique for mapping the white matter of the brain. DTI is a non-invasive method that generates images of white matter tracts (neuronal axons) by reflecting the diffusion of water

molecules in brain tissue (O'Donnell & Westin, 2011). It provides information on the structural connectivity of brain neural tracts, also known as tractography and DTI. DTI has high sensitivity in detecting microscopic abnormalities in tissue structure (Alexander et al., 2007). The direction of water diffusion provides significant information about connectivity between surrounding tissues or brain regions. A disconnection theory in schizophrenia states that it is caused by failed or abnormal communication between brain region structures (spatially) (Alexander et al., 2007; Whitford et al., 2011).

Studies of cognitive function with the application of DTI are limited, as not many research studies have yet been published. However, there is growing evidence that DTI can be used to identify connectivity changes in default mode or resting state networks in schizophrenia. The earliest study of DTI in schizophrenia was conducted by Buchsbaum et al. in 1998. They found that schizophrenic patients had significantly reduced fractional anisotropy (FA) in several white matter tracts, including the superior and inferior longitudinal fasciculi, the cingulum bundle, the fornix, the corpus callosum, and the arcuate fasciculus.

Another study was done by Buschsbaum et al. (2006), in which they acquired 64 schizophrenic patients to investigate the changes in axonal white matter alignment in the frontal and frontotemporal regions. They used significant probability mapping to compare the changes between the two groups. They discovered anisotrophy reduction across the frontal and callosal regions, where the widespread white matter region was prominently identified. Another study was done to identify the relation between DTI and the symptoms of schizophrenia. They recruited 25 schizophrenics and healthy controls and compared their DTI images to find the white matter integrity across symptoms of schizophrenia using PANSS (Skelly et al., 2008). They identified that there was a disconnection of brain regions with a reduction in diffusion and an inverse relation between DTFA and positive symptom scores. Even though this study does not directly indicate the cognition of schizophrenics, it does give an insight into brain disconnection related to positive symptoms.

This abnormality in anatomical or structural connectivity was consistently parallel to findings made by Yan et al., in 2012, that investigated the structural and functional connectivity in 33 schizophrenic subjects using resting-state fMRI and DTI. They further correlated the neuroimaging data with the cognitive test (Stroop test performance) and PANSS. The results showed significant abnormalities in both functional and structural connectivity of the ACC, with decreased positive connectivity to the bilateral putamen and caudate. In addition, the left posterior cingulated cortex showed increased negative connectivity, and the contralateral inferior frontal gyrus showed increased connectivity asymmetrically. With regard to the correlation between

the cognitive test and Stroop performance, the results revealed abnormalities in the structural and functional connectivity of the anterior cingulate cortex with the Stroop scores and the symptoms of schizophrenia in the patient group. This study provides evidence that cognitive impairment in schizophrenia is closely related to abnormal connectivity in structural and functional brain regions, especially in the ACC (Yan et al., 2012). Kochunov et al. (2017) did provide the supporting data to support the abnormality in connectivity and cognition among schizophrenics. His findings were parallel to his hypotheses, whereas schizophrenic patients did possess significantly lower whole-brain mean FA, processing speed, and working memory with Cohen d = 0.63; $p < .001$; Cohen d = 1.24; $p < .001$; and Cohen d = 0.83; $p < .001$, respectively. Besides, processing speed and working memory do have a correlation with the FA value. Thus, it was concluded that schizophrenia does relate to a white matter deficit with a significant negative influence on working memory and speed processing.

This research finding was consistent with a previous study by Nestor et al. (2004), which compared 41 schizophrenic subjects to 46 healthy control subjects in memory, intelligence, and executive function. They further correlated the neuropsychological data with the DTI findings and identified lower levels of declarative episodic verbal memory correlated with reduced left uncinate fasciculus (UF) and reduced left cingulate bundle (CB), which were highly correlated with executive function errors among schizophrenics compared to the control group (Nestor et al., 2017). As we can see from these few studies of DTI among schizophrenic patients, it is suggested that dysconnectivity between brain regions was established among patients, but the location of connectivity varied between studies. This variation could be confounded by factors such as severity of the disorder and medication status. It is expected that future researchers will investigate cognitive connectivity between spatial regions of the brain by using DTI tests, as not many studies are being published at the moment.

7. Neuropsychological tests

A neuropsychological test is a subjective test used to assist in the diagnosis of disorders related to cognitive, motor, behavioral, linguistic, and executive functioning (Butler-Pagnotti et al., 2023). The data obtained from this test can provide information that can assist in the diagnosis of a cognitive deficit or the confirmation of a diagnosis, as well as the localization of organic abnormalities in certain brain areas (Stroescu & Baughman, 2019). The data can also guide effective treatment methods for the rehabilitation of impaired patients. There

are many types of neuropsychological tests that assess different targets of cognitive abilities, such as intellectual functioning, language processing, attention, verbal learning and memory, visual learning and memory, executive function, speed of processing, sensory perceptual function, motor speed and strength, motivation, and personality (Kolb & Whishaw, 2009). In this review, three domains of cognitive function were critically discussed among schizophrenics: executive function, working memory, and speed processing. Each cognition was studied using different types of neuropsychological evaluations. Different neuropsychological tests offer complementary baselines to illustrate the general function of executive function among schizophrenic patients.

7.1 Wisconsin Card Sorting Test

The Wisconsin Card Sorting Test (WCST) was developed to assess a person's ability to adapt their strategies in response to changing stimulus conditions to achieve certain goals. It is recommended as a specific test for localizing prefrontal lobe dysfunction (Siddiqui et al., 2008). In schizophrenia, the prefrontal lobe is speculated to be affected the most compared to other brain locations, due to obvious defects in cognitive abilities such as blunted affect, an inability to organize and plan, and irrelevant thinking (Weinberger et al., 1994).

Prentice et al. (2008) studied the ability of 145 schizophrenic patients to use feedback in guiding behavior. The results showed that they performed poorly on pre-shift WCST trials, which signified an impairment in the ability to use feedback to guide behavior. Decreased maintenance of feedback-guided behavior is commonly found in schizophrenia patients, as they no longer have flexibility in changing strategies. Tallent and Gooding (1999) studied working memory among psychosis-prone individuals by separating them into two different groups: those with extremely high scores on the Social Anhedonia Scale (SocAnh; n = 49) or deviant scores on the Perceptual Aberration-Magical Ideation Scales (Per-Mag; n = 66). Both groups displayed subtle spatial working memory impairments compared to healthy adults. Their working memory was assessed on sensorimotor, degraded stimulus, and delayed response tasks, and the outcomes showed no significant differences between the psychosis-prone groups (Tallent & Gooding, 1999).

7.2 Controlled Oral Word Association test

The Controlled Oral Word Association Test (COWA) is used to evaluate subjects with a potential mild decline in cognition, especially in semantic fluency performance (Malek-Ahmadi et al., 2011). This test is rarely conducted among schizophrenics, which explains the limited research being conducted

using this test. The COWA test utilizes both executive and language function, with no dominant overlap between the two, due to their similar mediation structure function (prefrontal cortex and temporal lobe) (Malek-Ahmadi et al., 2011). In the COWA test, the subjects are asked to list out a verbal list of words according to an alphabet list given by the researchers (P, A and S). The verbal list must be in a specific category determined prior to the session. Each listing session lasts for 5 minutes, and the scores are assessed based on the verbal word counts.

Schizotypal disorder, a mild type of schizophrenia, showed satisfactory performance in verbal fluency, but as the task became more challenging, a deficit in their attention and verbal fluency was observed (Voglmaier et al., 2000). Kake et al. (2016) further investigated the executive function among 54 schizophrenic patients by incorporating 7 different kinds of neuropsychological assessment (including the COWA test) in order to have a complementary view of executive function among schizophrenics by comparing it to that of healthy control subjects. Their findings indicated significantly lower verbal fluency across the target groups, with no significant difference in attention skills.

7.3 The Stroop test

The Stroop test was conventionally used in attention assessment in a clinical setting. Wide research has been done on evaluating executive function by implementing this test in their research. This test embraces card manipulation techniques with a 3-condition session whereby the subjects have to subjectively respond to instructions given: (a) word reading, subjects read black ink words on cards; (b) colour naming, subjects verbally name symbols on cards; (c) colour word naming, the colour and words incongruently mismatch (ex: "blue" printed in green colour). The overall scores were obtained based on correctly completing the task within the specified time. The Stroop test does not only measure frontal lobe function in manipulation but also speed of processing towards a differential task. Schizophrenics tend to have slowed processing times or reaction times (RTs) and poor manipulating skills due to their limited function in giving attention (Perlstein et al., 1998). This phenomenon is known as the "Stroop effect", where subjects are not able to perform an interference or manipulated task that consists of relevant and irrelevant words (Grapperon & Delage, 1999; Hepp et al., 1996). One of the earliest studies in speed processing among schizophrenic patients was made by Wapner and Krus (1960), whereby they revealed significant delays in RTs among 24 schizophrenics at all 3 conditions of the Stroop tests. As for recent findings, longitudinal follow-up on 56 schizophrenic subjects identified the Stroop effect in longer-medicated groups compared to earlier stages of medication. Even though this study was influenced by medication factors, it does reflect the

persistence deficit of stroop effects in schizophrenia (Chen et al., 2001). In contrast, Henik and Salo (2004) explained that the Stroop test in interference sessions does give a Stroop effect among schizophrenics; however, the level of attention was adequate for maintaining simple tasks such as colour coding and word coding sessions.

7.4 Working memory test (Spatial Span and Digit Span test)

Working memory is conceptualised as the online storage for visuospatial, audiospatial, and verbal information, whereby the memory may rapidly decay if not repeatedly rehearsed into long-term memory (Conklin et al., 2005). This type of memory is highly related to the short-term memory used in manipulating tasks. Schizophrenia is a well-known disorder with defects in working memory performance, as people with schizophrenia have limited capabilities in performing certain tasks that require them to use working memory skills (Cassetta & Goghari, 2016), such as in Spatial and Digit Span tasks (Bagramyan & Tremblay, 2017; Pukrop, 2003). The digit span task test comprises two types, which are the backward and forward tests. The Digit Span test requires subjects to hold given information and asks them to sort the information in a specific order, whether in a backward or forward direction. Perry et al. (2001) performed working memory research in schizophrenics by comparing both types of the Digit Span task among 50 schizophrenic patients and 50 normal subjects. He expected poor performance in backward recall working memory; however, the findings revealed an equivalence deficit in both forward and backward digit span tasks among schizophrenics compared to healthy subjects. Another study in regard to spatial working memory deficit was found by Park and Holzman (1992), who demonstrated impairment of spatial delayed response in a Digit Span task among schizophrenics compared to healthy and bipolar disorder groups (Park & Holzman, 1992). They further claimed that the deficit in functioning of the dorsolateral prefrontal cortex in schizophrenics may limit neural functioning in sensory control tasks and manipulation of working memory tasks. Manglam et al. (2010) studied the working memory in schizophrenic patients, whereby they infused both the spatial span forward task and the spatial span backward task in their study. His research team identified that the impairment of working memory was significantly greater in schizophrenics when manipulating working memory tasks compared to control subjects, indicating that both domains of auditory and visuospatial working memory were equally affected in schizophrenics.

8. Conclusion

This mini-review offers a comprehensive discussion of cognitive function studies in schizophrenia, incorporating insights from multimodal neuroimaging and neuropsychological test studies. Findings from neuropsychological tests consistently demonstrate that individuals with schizophrenia exhibit abnormal cognitive processing across various tasks. These impairments are predominantly attributed to deficits in working memory, attention, and the ability to manage tasks effectively. In relation to these cognitive abnormalities, neuroimaging studies have revealed structural abnormalities primarily in the prefrontal cortex, as identified through MRI. However, findings on functional connectivity abnormalities have been inconsistent, with variability in connectivity strength across studies. This highlights the need for further, more in-depth research to address these inconsistencies and deepen our understanding. The rationale for integrating multimodal neuroimaging and neuropsychological assessments in this review is to establish a clear connection between behavioral outcomes and brain abnormalities in schizophrenia. Neuropsychological evaluations provide insights into behavioral deficits, while neuroimaging sheds light on structural and functional disruptions in the brain. Together, these tools offer complementary perspectives, elucidating the relationship between brain activity abnormalities and observed behaviors in schizophrenia. Therefore, this mini-review serves as a valuable resource, presenting an organized overview of current findings in a single article. By synthesizing information from these two domains, it highlights the importance of combining methodologies to advance our understanding of schizophrenia's impact on the brain and behavior.

Acknowledgement

The authors gratefully acknowledge Universiti Malaysia Sarawak (UNIMAS) for its support in this work.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of interests

The data underlying the discussion presented in the study are available from Dr. Siti Atiyah Ali (asatiyah@unimas.my) on request.

Data accessibility

The data presented in this study are available on request from the corresponding author due to ethical reasons for sensitive personal data protection (requests will be evaluated according to the GDPR - Reg. UE 2016/679 and its ethical guidelines).

Author contribution

Development and conceptualization: S.A.A., N.A.A.A., Z.I., N.A.F.
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