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Verbal memory deficits in schizophrenia

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Abstract. Schizophrenia is a severe mental disorder characterized by multifactorial etiology, encompassing genetic and environmental risk factors, as well as structural brain abnormalities. The disorder manifests through a spectrum of symptoms, broadly categorized as positive, negative, and cognitive impairments. Among these cognitive deficits, verbal memory impairment stands out as a substantial and pivotal symptom of schizophrenia, significantly predicting future functional outcomes. This deficit primarily arises from a substantial decline in encoding ability coupled with a mild increase in forgetting rate. To assess the extent of this impairment, word list learning tasks are commonly employed. Research has established a clear association between verbal memory deficits and alterations in hippocampal volume, aberrant brain responses, and anomalies in spontaneous brain activity. Although targeted pharmacological interventions for verbal memory deficits are currently lacking, medications aimed at enhancing cognitive function, such as aripiprazole, present a viable interim option. Future research endeavors should focus on exploring the fundamental aspects of memory and brain structure and function, while incorporating advanced techniques like repetitive transcranial magnetic stimulation (rTMS) into investigations of verbal memory deficits. Additionally, the development of animal models capable of simulating verbal memory deficits holds promise for advancing our understanding of this critical aspect of schizophrenia.

Keywords: Schizophrenia, Cognitive Impairments, Verbal Memory Deficits, Clinical Treatment.

1. Introduction

Schizophrenia, a severe and enduring mental illness, finds its roots in ancient history, with early descriptions bearing a striking resemblance to the condition dating back to 1550 BCE in the Ebers papyrus of Egypt. A century ago, Emil Kraepelin first provided a comprehensive account of schizophrenia's symptoms, characterizing it as "dementia praecox," [1] a term attributed to Benedict A. Morel [2]. With a lifetime prevalence of approximately 1% [3], coupled with a heightened risk of suicidality and multifaceted deficits, including cognitive impairments, schizophrenia has been a paramount focus of research within both academic and clinical realms. The etiology, clinical diagnosis, and treatment of schizophrenia have been central themes in this research, driven by a belief in its multifactorial origins. Factors contributing to schizophrenia encompass genetic predisposition, environmental influences, structural brain alterations, neural depth pathology hypotheses, and neural-immune abnormalities. Notably heritable, schizophrenia can be triggered by environmental risks, with underlying genetic factors exerting variable influences. Strikingly, an average concordance rate of 50% exists among identical twins, whereas genetic divergence suggests a concordance rate of 100% [4]. Environmental factors contributing to schizophrenia include psychosocial stressors, stemming from

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family dynamics, and biological factors such as complications during pregnancy and malnutrition. Structural brain anomalies, resulting from neural developmental errors or other traumatic incidents, may also play a role in the onset of schizophrenia. For instance, injuries to the hippocampus or cerebral cortex have been associated with the induction of schizophrenia. Additional risk factors encompass medication use, abnormalities in neurotransmitter systems, and disruptions in signal pathways, as well as aberrations in brain immune functions.

The symptomatic manifestations and impairments seen in schizophrenia can be broadly categorized into positive symptoms, negative symptoms, and cognitive impairments [5]. Examples within each category include positive symptoms such as hallucinations and delusions, negative symptoms like apathy and social withdrawal, and cognitive impairments that impact intelligence and memory function [6]. Symptomatology may exhibit considerable variability among patients, with no single symptom being obligatory. However, it is well-established that up to 75% of individuals with schizophrenia experience substantial cognitive deficits [6]. Intriguingly, the mechanisms underlying the onset of cognitive impairments [7] and their potential treatments remain areas of active investigation, as current therapeutic approaches for schizophrenia have demonstrated limited efficacy in improving cognition [8,9]. Cognitive impairments in schizophrenia can be broadly classified into three domains: basic visual and auditory perception, non-social cognition (also known as neurocognition), and social cognition. Patients with cognitive dysfunction often exhibit impaired social functioning, which can be attributed to deficits in both social cognition and fundamental cognitive functions, underscoring the prominent role of cognitive impairments in the social dysfunction observed in individuals with schizophrenia [10].

Given the intricate nature of cognitive functions, some argue that no distinct domains can be unequivocally delineated within the realm of cognitive impairments in schizophrenia [7]. A limitation in precisely specifying functional domains often leads to the derivation of a composite neurocognitive factor score, encompassing all neurocognitive domains [9]. Nevertheless, memory impairment emerges as one of the most prevalent cognitive deficits in schizophrenia. Within the domain of memory-related factors in neurocognition, verbal memory, visual memory, and working memory are pivotal components, with their dysfunction identified as a core feature of schizophrenia [9, 11]. Learning, frequently intertwined with memory, encompasses both verbal and visual learning. Among these cognitive facets, memory, a subject that has captivated scholars and philosophers for centuries, holds a prominent position, with verbal declarative memory emerging as one of the most substantial memory deficits in schizophrenia. This critical area warrants further exploration and investigation.

2. Current understanding of verbal memory deficits

Verbal declarative memory impairment represents one of the most prominent memory deficits in individuals with schizophrenia, with visual memory being the other major area of concern. Researchers have discerned that the families of schizophrenia patients are more profoundly affected by deficits in verbal memory compared to visual memory [12, 13]. This striking finding underscores the critical role of verbal memory deficits as a hallmark symptom of schizophrenia. Importantly, these deficits tend to manifest early, often persisting from the first episode and remaining persistent even as the condition becomes chronic [14]. This persistence mirrors the early, predominant, and progressive reduction in hippocampal volume observed during adolescence [12]. Verbal memory deficits have a profound impact on verbal learning, rendering it the most compromised cognitive domain throughout the course of schizophrenia [15]. While some aspects of these deficits may not be as severe as those observed in other memory-affecting conditions, such as Alzheimer's disease, it is noteworthy that patients with schizophrenia often exhibit impairments in delayed recall and information storage, indicating a comprehensive memory deficit [14]. The profiles of these two groups, though differing in severity, share notable similarities. Currently, no targeted and effective treatment specifically addressing verbal memory deficits in schizophrenia exists [14, 15]. Moreover, prolonged use of antipsychotic medications may exacerbate these deficits. While certain antidepressants capable of elevating gamma-aminobutyric acid (GABA) levels may offer some assistance in long-term memory encoding and retention, the need for more direct and specific medications is evident. Consequently, the academic research community

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has dedicated substantial attention to exploring the nuances of verbal memory and learning in schizophrenia. Verbal recall serves as a fundamental measure to assess these abilities, with impaired free recall indicating an inability to access stored information. Inefficiencies in the verbal encoding process for long-term memory are often reflected in recall deficits. Researchers have identified that the impairment in the learning process is the primary influential factor contributing to verbal recall deficits, with a higher rate of forgetting playing a secondary role [12, 14].

The most widely adopted method for assessing verbal memory deficits involves administering a series of word list learning tasks, such as the Rey Auditory Verbal Learning Task (RAVLT) and the California Verbal Learning task, which yield immediate and delayed recall test scores [15]. Controversies persist regarding the potential impact of repeated participation in verbal memory tests on patient performance. Longitudinal studies have reported varying results, with some suggesting improvements in immediate recall over time, while others have observed deterioration in verbal memory among patients subjected to repeated testing [14]. In examinations of thirty-minute delayed recall, individuals with schizophrenia consistently demonstrate reduced information retention compared to healthy controls [13]. Furthermore, studies have revealed that the pattern of verbal recall deficits is not uniform but exhibits a clear and robust familial pattern. This pattern extends to family members, such as siblings, who can be evaluated for potential schizophrenia morbidity based on these deficits [13]. In the course of these memory tasks, it is essential to employ neuroimaging techniques to elucidate brain activation and stimulation patterns. Functional magnetic resonance imaging (fMRI) has been instrumental in this regard, offering insights into brain responses during verbal memory-related tasks [16]. Although not all hypotheses regarding the relationship between activation and recall performance have been fully substantiated, fMRI studies have identified common clusters in frontal and temporal brain regions associated with superior recall performance. Notably, an under-activation in the ventrolateral prefrontal cortex has been observed in individuals with schizophrenia, potentially contributing to their verbal learning deficits.

The hippocampus, a region of considerable interest in memory research within the context of schizophrenia, has also been examined for differences in brain responses between patients and healthy controls. While no statistically significant differences in recall performance have been observed overall, the pattern indicates that schizophrenia patients exhibit significantly stronger task-related responses in the right hemisphere, particularly in the anterior region [16]. Additionally, the left posterior cluster in the hippocampal region shows significantly reduced activity in schizophrenia patients, albeit without a significant correlation with recall performance. Moreover, research has consistently demonstrated a negative relationship between verbal recall performance and hippocampal volume [12, 15], with a positive correlation existing between performance on the Hopkins Verbal Learning Test-Revised (HVLT-R) and bilateral hippocampal volumes among patients. These findings suggest that reduced hippocampal volume is a key contributor to the impairment in verbal memory, characterized by both immediate and delayed verbal learning deficits. Furthermore, significant gray matter loss in other brain regions, including the frontal, temporal, and parietal areas, has been observed in individuals with schizophrenia compared to both atypical psychoses and healthy controls [12].

An area of particular interest is the inferior frontal gyrus, where task-related active response clusters have been identified in both healthy controls and schizophrenia patients. Nevertheless, schizophrenia patients exhibit abnormal responses in the bilateral ventrolateral regions, especially on the right side [16]. During the learning process, the brain response in this region is less active, with fewer areas showing preferential involvement compared to the fixation state, indicating aberrations in these processes. Furthermore, the positive task-related response observed in parietal and frontal clusters in healthy controls is largely absent in patients, and the response in the left fusiform temporal gyrus of patients is consistently lower than normal [16]. Overall, schizophrenia patients exhibit under-activation in the right anterior cingulate, right dorsolateral and anterior prefrontal regions, and the left lateral temporal cortex [14] during their participation in a verbal paired-associates learning task. These observations may be explained through the lens of brain radiation. In a study by Tanaka-Koshiyama *et al.*, resting-state electroencephalography (EEG) was employed while subjects underwent various tests,

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including the California Verbal Learning Test second edition (CVLT-II). The most robust association between brain radiation and verbal learning ability was established in the frontal region of the brain [17]. Notably, schizophrenia patients exhibited elevated levels of alpha, beta, gamma, and theta frequency bands compared to healthy controls. This contrasts with previous research indicating increased gamma power at the occipital cortex in first-episode patients and decreased power at the prefrontal cortex in first-episode patients, with an expansion to temporal and sensorimotor cortices in chronic patients. These disparities may be attributed to differences in clinical stages among subjects. Specific regional gamma associations were established at three electrodes on the right frontal-temporal region. Schizophrenia patients exhibited significant negative and positive correlations between gamma-band activity at FP2 and at F4 and T8, respectively, and verbal learning ability. This suggests that heightened radiation levels may generate high-frequency cortical noise, contributing to deficits in verbal learning.

3. Discussion

Cognitive impairments in schizophrenia represent a critical challenge in the treatment of this complex disorder. Given the intricate nature of cognition and the brain systems involved, there is currently no optimal medication available for addressing cognitive and negative symptoms. Alarmingly, some of the primary treatments for schizophrenia, which target positive symptoms, may exacerbate cognitive deficits. Among these cognitive symptoms, verbal memory and learning deficits are particularly severe and persistent, demanding therapeutic intervention.

The pathogenic mechanism underlying verbal learning deficits in schizophrenia can be characterized by a significant decline in encoding ability, coupled with a mild increase in the rate of forgetting. This suggests that individuals with schizophrenia learn information at a slower pace and forget it more rapidly [14]. Two potential medical interventions can be considered: enhancing the speed and capacity of memory acquisition and slowing down the rate of memory deterioration. Ongoing research is focused on developing novel medications that can address not only positive and negative symptoms but also cognitive impairments. In the interim, a viable approach is to utilize medications that have demonstrated efficacy in improving cognitive functions, such as aripiprazole, a serotonin-dopamine system stabilizer known to alleviate affective and cognitive impairments. Complementary medications with minimal cognitive side effects may also be incorporated as needed.

An alternative avenue for treatment could be informed by research findings. Scientists have identified several abnormalities in schizophrenia patients compared to healthy controls and those with atypical schizophrenic psychosis. Notably, hippocampal volume reduction is most prominent in early adolescence and is considered a significant contributor to verbal memory deficits. Given the current understanding of the hippocampus's role in memory storage and the importance of verbal learning in emotional expression [12], further research in this area holds promise. While regular physical exercise has been shown to enhance hippocampal volume, ongoing fundamental research may eventually lead to interventions such as surgery to reverse the pathologically significant reduction in hippocampal volume [18].

Beyond structural changes in the hippocampal region, schizophrenia patients exhibit altered brain responses in multiple brain regions, indicating non-structural functional changes. While conflicting results have been reported, likely due to variations in the stage of illness, clinicians can assess patients for response abnormality profiles and consider the placement of multiple electrodes to control and regulate these abnormalities. Although invasive electrode placement may not be a feasible option in the foreseeable future, non-invasive brain stimulation methods hold promise for alleviating symptoms. Current knowledge of brain structure and function may not yet be robust enough to delve into the finer details of this clinical approach. Furthermore, gamma-band abnormalities have been identified in schizophrenia patients. Researchers have applied repetitive transcranial magnetic stimulation (rTMS) to probable Alzheimer's disease patients, resulting in significant cognitive improvement [19]. TMS-derived measures have also been suggested as predictors of deterioration. Given the similarities between Alzheimer's disease and schizophrenia patients in terms of verbal memory profiles, rTMS could become a prominent treatment for this symptom in the near future.

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Schizophrenia, due to its limited range of onset in species, has been challenging to study in animal models, leading to a lack of experiments that can be conducted solely on animals such as rats and mice. However, scientists have identified medications that can induce psychosis-like symptoms. It is, therefore, feasible to develop a medication and employ various techniques to induce similar brain response differences in animal subjects compared to healthy controls. This could ultimately lead to the creation of animal models that simulate verbal memory deficits in schizophrenia, enabling further research in this area. Additionally, since linguistic functional disorders in humans cannot be effectively replicated in animals, there is a pressing need to develop animal models specifically designed for verbal memory research. Given their higher genetic similarity to humans, primates may offer the most promising avenue for developing such models.

4. Conclusions

Verbal memory deficits represent one of the earliest onset symptoms and serve as potent indicators of the future development of schizophrenia in individual patients. Their occurrence can be attributed to various factors, such as alterations in hippocampal volume, abnormal brain responses, and aberrant brain radiation. Given the absence of a singular medication designed specifically for addressing this issue, it is advisable for patients to consider pharmaceutical interventions that can enhance cognitive functions, in conjunction with other necessary treatments. Moreover, it is imperative for the academic community to expand its focus beyond clinical research on memory deficits, encompassing the development of animal models that can effectively mimic the linguistic symptoms of schizophrenia, thereby facilitating more comprehensive investigations in this domain.

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