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Schizophrenia and Time Perception: A Systematic Review

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Abstract:

Introduction: Schizophrenia, a neuropsychological condition characterized by a spectrum of positive and negative symptoms, presents a unique challenge in understanding its underlying mechanisms. Among the myriad symptoms, disturbances in time perception have garnered attention for their potential insights into the disorder's pathophysiology. This comprehensive review delves into the intricate association between schizophrenia and time perception, synthesizing evidence from diverse research domains.

Methodology: Methodologically, a rigorous literature review encompassing cohort studies, randomized controlled trials, and other relevant investigations conducted between 2000 and 2023 formed the basis of this analysis.

Results: The results reveal consistent findings of impaired time perception among schizophrenia patients, manifested in altered abilities to estimate time intervals and discriminate temporal stimuli. Neurobiological correlates, including disruptions in neurotransmitter pathways and structural changes in key brain regions, shed light on the underlying mechanisms of temporal dysfunction in schizophrenia. Moreover, cognitive impairments, such as deficits in attention and working memory, are implicated in exacerbating time perception deficits in this population. The implications of these findings extend to diagnostic approaches and therapeutic interventions, emphasizing the importance of considering time perception abnormalities in the clinical management of schizophrenia. Furthermore, the discussion highlights the need for further research to elucidate the causal relationship between schizophrenia and time perception and to explore targeted interventions aimed at mitigating temporal dysfunction in affected individuals.

Conclusion: This review underscores the multifaceted nature of schizophrenia and underscores the potential of time perception as a promising avenue for advancing our understanding and treatment of this complex disorder.

Keyword: Schizophrenia, Time Perception, Neuropsychological Impairments, Cognitive Processes

I. INTRODUCTION

Schizophrenia is a neuropsychological condition that encompasses a vast majority of positive and negative psychosocial symptoms such as hallucinations, delusions, and executive functions. The aetiology of this condition is linked to a constellation of neurological functions. One of the neurological functions that is significantly affected in schizophrenia is time perception. Time perception is the ability to correctly estimate time intervals. This phenomenon of time perception shares common neurotransmitter pathways with those that are affected in schizophrenia. The association of time perception and schizophrenia has been studied in many settings. However, the true relationship of its pathophysiology remains unknown (1). According to a study by Bonnet et al, people with schizophrenia tend to overestimate time intervals (2). This indicates the possible association of schizophrenia with time perception.

The understanding of this association can lead to better interventional strategies to cure schizophrenia (3). The temporal disorganisation of thoughts and behaviour in schizophrenia has been studied over time intervals, starting from their onset to maximal state. The fact whether wrong interpretation of time intervals by schizophrenic patients is associated specifically with schizophrenia or not is still under study. There is a possible association of time misperception with psychosis instead of schizophrenia itself (4). To understand whether all these possible theories of this association hold any substantial value or not, certain study models have been created to discern the true relationship between time perception and schizophrenia. Different parts of the brain cortex are involved in the pathophysiology of schizophrenia which also function for correct estimation of time. This could possibly open horizons towards understanding the correlation between them (5,6).

Certain studies have shown that these patients have a problem in coordinating time with a circumstance. The concept of time perception is not associated with any sensory organ by itself. Rather, it works by linking different levels of consciousness such as arousal and attentiveness (7). The purpose of our study is to establish a well-explained relationship between time perception and schizophrenia. Therefore, we are conducting a meta-analysis to understand the pathophysiology, neuropsychology and study models for schizophrenia.

II. METHODOLOGY

The systematic review was done adhered to the PRISMA reporting guidelines 2020.

Inclusion and exclusion criteria

Articles published in English, cohort studies, randomised controlled trials in or mental health disorders focusing on schizophrenia and time perception, and other studies that were dated between 2000 and 2023 were all considered for inclusion in the selection process. Reviews, abstracts, non-English literature, meta-analyses, case reports and reviews were excluded.

Literature review and study selection

Six investigators independently conducted the search in Pubmed, Google Scholar, Scopus. A comprehensive search query, using MESH strategy employing a combination of appropriate subject headings and keywords was developed, “Time” “timing” “schizophrenia” “time perception” was the search keyword we used in our study. The titles and abstracts of the papers were used to initially filter them; the screened articles were then chosen using the inclusion and exclusion criteria. Four investigators workedindependently on this process, with the other two investigators resolving any differences. Study selection occurred in two successive rounds, the first round based on titles and abstracts, the second round based on full text. We further narrowed them by adding our selection criteria to an AI-powered program named "Rayyan" after importing all of the articles.

Data collection

Five review authors independently gathered pertinent study features and outcomes from the included studies using standardised and piloted data extraction forms. The following data were taken from each study: author, year of publication, characteristics of participants (number, age and sex), study design, study tools, study period, intervention and result. Any discrepancies about date extraction were resolved among the authors. The study was conducted through November 2023 to December 2023.

Outcome measures

The outcome measure is to assess the impact of the disorder on various neuropsychological aspects related to time perception. This includes evaluating pathological mechanisms underlying time perception deficits in schizophrenia, as well as examining different study models employed in research to understand these phenomena.

Statistical analysis

Analysing existing literature elucidates the intricate relationship between schizophrenia and alterations in time perception. Various study models, ranging from neuroimaging techniques to behavioural assessments, are scrutinised to understand the neural mechanisms and cognitive processes implicated in temporal dysfunctions associated with schizophrenia. ROB assessment and heterogeneity assessment has been conducted.

III. RESULTS

A total of 2173 articles were identified from various databases for the review. After removing duplicate articles and conducting an initial eligibility assessment, 226 articles remained. From these, 61 articles were sought for retrieval, and only 38 were retrieved. Among these 38, 22 did not meet the inclusion criteria, leaving 16 studies eligible for inclusion in the study as seen in figure 1.

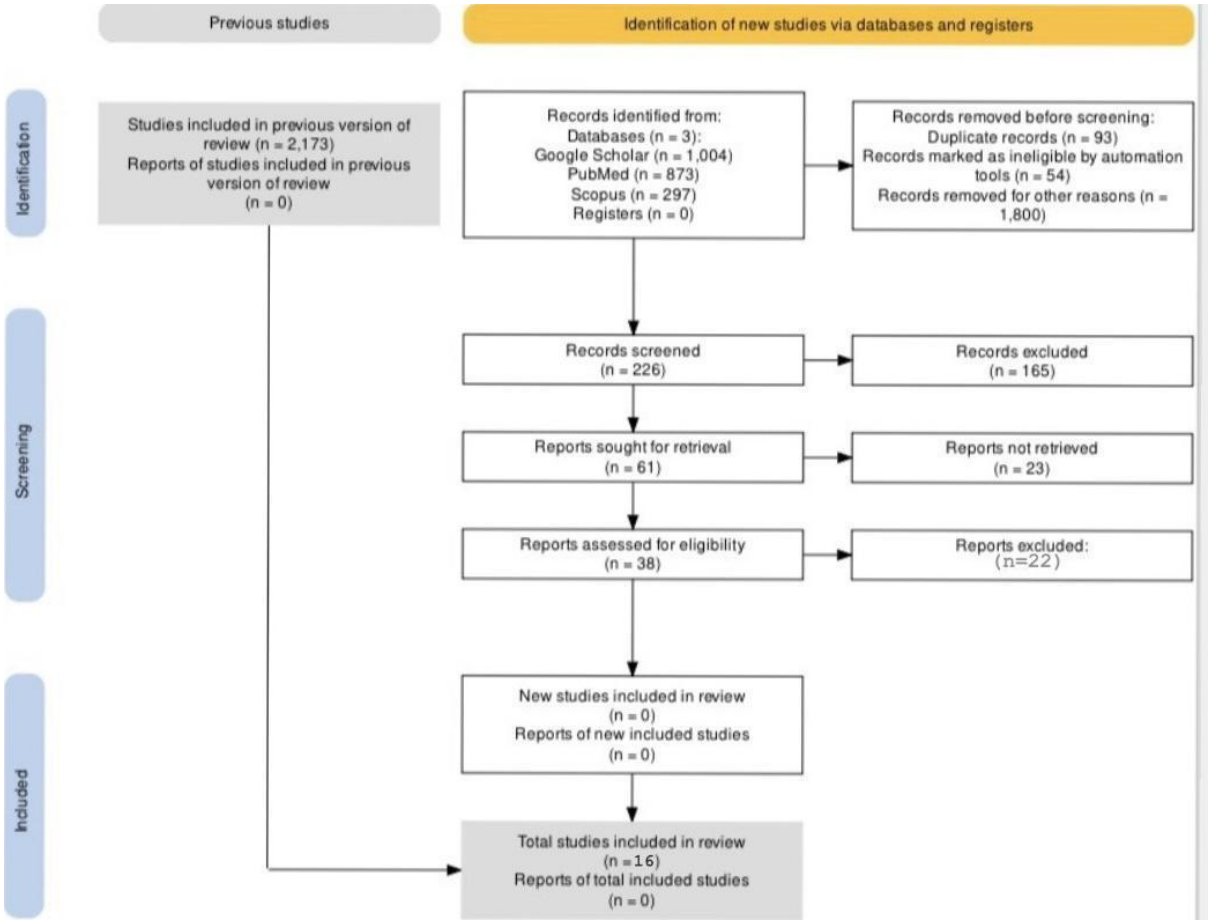

Figure 1: PRISMA flow chart for study screening and selection

Findings

Schizophrenia patients exhibited impaired performance in discriminating tone durations compared to normal controls, and neuroanatomical regions associated with temporal processing (supplementary motor area, striatum, and insula/opercula) displayed signs of dysfunctionality. Dysfunctions in neural circuits, such as those involving

dopamine, can result in disruptions to both cognitive processes (e.g., working memory) and time perception (e.g., interval timing). Essentially, these mental processes share overlapping neural underpinnings.

In a study, a transgenic mouse model was used to selectively overexpress D2 receptors in the striatum. The results indicated that this overexpression led to a decrease in operant response rate, a widening of the distribution of operant responses over time, and an increase in the latency of the peak in response rate. Conversely, turning off D2 overexpression resulted in an improvement in both response rate and the accuracy of timing. In other studies, interactions between ANKK1 and MAOA with COMT1 are established (2).Brain lesion and neuroimaging investigations have revealed that the key brain structures involved in time perception encompass the right-lateralized prefrontal and parietal lobes, thalamus, basal ganglia, and cerebellum. These areas have been implicated in the pathophysiology of schizophrenia, where there is observed impaired coordination of activity among these regions. The findings from multiple studies indicate that individuals with schizophrenia tend to overestimate the passage of time and exhibit less accuracy in time estimation tasks compared to their healthy counterparts.
Various findings indicate that time misperception in schizophrenia may not solely result from a malfunction in the time processor. Impaired attention and memory, which are integral to time estimation, serve as confounding factors in both schizophrenia and time perception.(1)Participants were able to differentiate between the ‘‘short’’ and ‘‘long’’ anchor tones with a 75% accuracy rate by the end of the practice session. Schizophrenia, schizoaffective disorder, and bipolar disorder with psychotic features (but not bipolar disorder without psychosis), would show increased temporal variability compared to healthy controls.(3)Individuals with SZ utilised predictive mechanisms for socially relevant stimuli, such as auditory sequences. Individuals with SZ exhibited impaired phase-shift detection for intervals ranging from 300 to 900 ms, suggesting a deficit in predictive timing mechanisms.
The dissociation between impairment in timing error detection and normal serial interval production in SZ suggests involvement of distinct neural circuits for predictive timing and interval production. Linear regression analyses on Inter Tap Intervals (ITIs) revealed that PANSS-N (negative symptoms) predicted produced periods at slow rates in SZ (8).

Time perception performance in SZ is strongly associated with well-known disorder-related cognitive impairments. Patients were less accurate than controls in discerning both temporal and non-temporal stimulus attributes, indicating a general disturbance in discrimination behaviour in SZ. Temporal sensitivity deficits in SZ are correlated with working memory(WM) accuracy, suggesting that timing deficits are a side effect of a more fundamental WM impairment. Duration estimation impairments seem to be underpinned by deficits in concurrent cognitive processes rather than a genuine time perception deficit.SZ patients exhibit a dissociation in temporal and spatial invalidity effects, suggesting difficulties in combining acquired knowledge about the predictive value of informative signals with sensory evidence. Patients rely more on sensory data than informative cues, leading to potentially false inferences (9).

In individuals with schizophrenia, both transient and Steady-State Responses (SSR) at 25 Hz show lower amplitude compared to controls. The Phase-Locking Factors (PLF), indicating neocortical synchronisation in response to tactile stimuli, are significantly reduced in schizophrenia, suggesting a deficit in accurately reflecting the timing of incoming sensory stimuli.The impaired timing in the somatosensory cortex of individuals with schizophrenia may impact the regulation of motor behaviour. This deficit could contribute to impaired coordination of gross motor behaviours and may influence the accuracy and interpretation of the corollary discharge generated by the motor cortex, potentially leading to hallucinatory experiences.
Decreased amplitude and lower PLF of SSR in both auditory and visual domains suggest a possibility of a common timing impairment across sensory cortices in schizophrenia. The thalamus or the cerebellum, as common circuit elements, may also be compromised, contributing to the observed deficits (10).The review suggests that deficits in cognitive processes, particularly working memory and sustained attention, can result in impaired interval timing in individuals with schizophrenia. Deficient temporal information processing is proposed to contribute to positive symptoms of schizophrenia, such as delusions and disorganised behaviour.

Distorted timing may lead to a failure to correctly perceive the temporal sequence of events, contributing to symptoms like paranoid delusional thinking.

The critical role of dopaminergic signalling in interval timing is highlighted, and the documented dopaminergic dysfunction in schizophrenia is considered in the context of aberrant attribution of incentive salience and abnormal reward processing (11).

Study models used in the studies were:

SAPS and SANS Models:
The study utilises the Schedule for the Assessment of Positive Symptoms (SAPS) (17) and Schedule for the Assessment of Negative Symptoms (SANS) to evaluate symptom severity in schizophrenia (12)(24).

Implicit and Explicit Time Concept:
It investigates the concept of implicit and explicit time to explain the development of symptoms in schizophrenia (13).

Movement Time Testing Model:
It tests patients using the time needed to complete a horizontal movement towards a target in response to visual stimuli (14).

EEG Changes and Schizophrenia Model:
It targets the association between EEG changes and schizophrenia, exploring how electroencephalogram alterations may be linked to the disorder (15).

Consensual Qualitative Research (CQR)
Deeply explore complex phenomena by gathering and analysing rich data from participant's perspectives (16).

Cognitive Neuroscience of Time Perception
Explore how the brain processes time, integrating cognitive psychology and neuroscience (25).

Psychometric Tools:
Utilises psychometric tools including Matlab, Brief Psychiatric Rating Scale (18)(19), Hamilton Depression Scale (21), Beck Depression Inventory(21), Scale for Assessment of Positive Symptoms, and Scale for Assessment of Negative Symptoms(19).
The SCoRS-J and BACS-J were used to assess cognitive functioning of the patients. The Global Assessment of Functioning (GAF) was used to assess social functioning(23).

Symptom Assessment Tools:
Employs the Positive and Negative Syndrome Scale (PANSS) to assess schizophrenic symptoms(14)(18)(20)(21)(23).
Assesses psychosocial functioning using the German version of the Personal and Social Performance (PSP) scale(21) and evaluates the general severity of illness with the Clinical Global Impression (CGI) scale(21).

Pathophysiology:

Neuropsychological impairments in schizophrenia manifest in altered time perception, with patients judging durations significantly shorter than control subjects, particularly in specific conditions. These findings underscore the link between time perception abnormalities and neuropsychological dysfunction, potentially impacting daily activities (12). Attentional and executive dysfunction further exacerbate time judgment difficulties, especially in patients with early-onset schizophrenia, correlating with impairments in attentional and

executive functions (20). Time perception in schizophrenia involves both implicit and explicit mechanisms, with implicit time relying on bodily functioning and affective synchronization, while explicit time involves desynchronization (13). The mesencephalic dopamine system and striato-prefrontal projections play a crucial role in time processing, potentially contributing to the acceleration of the internal clock observed in schizophrenia (14). Patients with schizophrenia also experience a loss of temporal continuity, contributing to subjective fragmentation along the temporal dimension (26). Cognitive impairment is a hallmark of schizophrenia, affecting various aspects of information processing, as assessed by neuropsychological test batteries commonly used in clinical settings (15,23). Imbalances in neurotransmitters, particularly dopamine and glutamate, as well as structural changes in brain regions crucial for temporal processing, contribute to disruptions in the perception and integration of temporal information (8). Aberrant functional connectivity within the brain's timing networks further exacerbates temporal dysfunction in schizophrenia, impacting the accuracy of temporal processing (27). First-rank symptoms, such as passivity experiences, are frequent in schizophrenia and are associated with time discrimination deficits, possibly mediated by dysregulation in dopaminergic pathways and abnormalities in the prefrontal cortex (24). Temporality is fundamental for the sense of coherence and continuity of selfhood, with disruptions in time experience leading to fragmentation and disturbances such as déjà vu and premonitions (16). Dopamine levels play a critical role in temporal precision, with elevated levels leading to reduced accuracy in time perception (28). Various models, including neurobiological internal clocks and linear/non-linear network models, contribute to understanding time perception in schizophrenia, reflecting the diverse experiences of time and the brain's adaptation to temporal scales (22).

ROB assessment of the 16 articles were done and computed in table 1.

Author	Rob score	Mean difference
Lee KH et al(12)	15	3.2916667
Fuchs T et al(13)	19	-0.7083333
Peterburs J et al(14)	18	0.2916667
Doege K et al(15)	12	6.2916667
Stanghellini G et al(16)	19	-0.7083333
Martin B et al(26)	21	-2.7083333
Roth M J et al(17)	16	2.2916667
Papageorgiou et al (18)	13	5.2916667
Sadibolova R et al (28)	18	0.2916667
Stevenson R A et al (19)	19	-0.7083333
de Montalenmbert M et al(20)	14	4.2916667
Mavrogiogou et al(21)	19	-0.7083333
Fontes R et al (22)	18	0.2916667
Masuzawa et al (23)	17	1.2916667
Waters F et al (24)	16	2.2916667
Wearden JH et al (25)	17	1.2916667
Mean score	16.9375	

IV. DISCUSSION

In the field of neuropsychology, the association of time perception with schizophrenia has been studied in detail. Due to its multifactorial nature, it is difficult to establish a simple causal relationship. Various neuropsychological pathways are involved in time processing some of which are common with pathways involved in schizophrenia(1). In patients of schizophrenia, there are problems with time judgement and executive functions. Neurotransmitters, especially dopamine and glutamate are affected in temporal processing. This forms the basis of the treatment plan for schizophrenia. Disruption in the internal clock of a person leads to the misinterpretation of the external world by the person. Impairment of episodic memory is attributed to abnormal interpretation of information at the encoding stage. Another study shows that the presence of mood and psychotic symptoms have a major impact on increased timing variability and decline in timed task performance(3). Further research on the possible organic level associations explains the link between symptoms of schizophrenia and changes in parieto-frontal monitoring circuit and cerebellum independently (8). These studies have explained the association between the changes that occur on a microscopic level in the brain which leads to the variety of symptoms of behavioural change and the diversifications among the causes of psychosis and their presentation.

While Bonnot et al. (2) was able to find clinical evidence relating time perception impairments in patients of schizophrenia across the cognitive, neuroscientific and psychological domains, they were unable to ascertain whether such impairments were due to the underlying disease process of schizophrenia or were due to coexisting memory and attention deficits in patients of schizophrenia (2). This emphasises the need for controlled studies to exclude the effect of memory-attention deficits as a possible cause for temporal impairments. Gómez et al. (1) considered the same domains as Bonnot et al. (2), however, they also included imaging findings and genetic hypotheses. The imaging findings did provide a neuroanatomical basis and the genes substantiated the neuropathological processes related to timing impairments in schizophrenia, however, they were also unable to distinguish memory and attention deficits as a cause of timing impairments (1). Ward et al. (11) used a mouse model to determine if timing intervals were due to underlying cognitive impairments of schizophrenia. They were able to rule out timing impairments due to decreased motivation, poor attention and poor working memory function and suggested that their findings could be applied to human patients of schizophrenia (11).

Bolbecker et al. (3), Turgeon et al. (8) and Teale et al. (10) performed controlled experimental studies to determine time perception impairments in schizophrenia. Bolbecker et al. (3) conducted a study to determine if psychosis was associated with timing impairments in patients of bipolar disorder, schizophrenia and schizoaffective disorder. While they were able to find increased time variability in both the bipolar disorder and schizophrenia groups, increased variability was present in the bipolar group irrespective of the presence of psychotic features. The schizoaffective group did not show any significant difference from the controls, thus partially invalidating the hypothesis proposed (3). The strengths of the study by Bolbecker et al. (3) was that they included reasonably large sample numbers and four clinical diagnostic categories with varying levels of psychotic and affective symptoms (3). One limitation that did stand out was the lack of concomitant psychosis and mood state information. Specifically, bipolar disorder patients had YMRS and MADRS data accessible, which offered an assessment of their present mania and depression symptoms, respectively, while schizophrenia and schizoaffective persons had PANSS data available, which assessed their current psychosis-related symptoms (3). Turgeon et al. (8) was able to control the effects of working memory towards time perception impairments and was thus able to empirically determine the existence of some low-level timing impairments in schizophrenia in their study. Teale et al. (10) was the only study that took into account the effect of antipsychotic medications on time perception along with other factors. Detailed studies have drawn the connection between the motor symptoms in schizophrenia patients and abnormal time perception in cortical responsiveness. In future, this can help us in curing the resistant symptoms as well. Time perception has also been used as a marker of illness severity. Due to the presence of impaired time processing in schizophrenia patients, many studies associate both to have a causal relationship (10). However, more evidence is required to establish a proper connection. At last, time perception and schizophrenia has been linked to each other at cognitive and clinical levels. The presence of abnormality in common pathways used for mood symptoms and

time processing further leads us to believe in the existence of a causal association.Schizophrenia, being a disorder of variable symptomatology, has been studied extensively to understand the actual cause of its development and progression. Certain types of positive symptoms are treatable while the other negative symptoms persist. Such findings force us to understand the causal relationship in more depth.

V. CONCLUSION

The review of the studies provide robust evidence of impaired time perception among schizophrenia patients, highlighting the complex interplay between neuropsychological impairments and neurobiological dysregulation. While further research is warranted to establish a causal relationship and explore therapeutic interventions, these findings underscore the need for comprehensive approaches to address the multifaceted nature of schizophrenia symptoms. Understanding the intricate relationship between time perception and schizophrenia holds promise for advancing diagnostic and therapeutic strategies.

STRENGTHS AND LIMITATIONS

Further behavioural and controlled studies are needed to better understand the timing deficits in schizophrenia. Variables such as age, sex, race, disease symptoms (positive or negative) and disease severity may play a role and should be considered in further studies. ROB of the study was low with highest ROB seen in the study by Doege K et al.(15)

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