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Evaluation and Treatment of Cognitive Dysfunctions in Schizophrenia and Bipolar Disorder

Şizofreni ve Bipolar Bozuklukta Bilişsel İşlev Bozukluklarının Değerlendirilmesi ve Tedavisi

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ABSTRACT

Cognitive dysfunction is the most important determinant for the recovery in schizophrenia and bipolar disorder. Cognitive dysfunction serves as an endophenotype although it may be a consequence of drug treatments. In schizophrenia starting from the first episode, pronounced cognitive defects such as cognitive flexibility, inhibition, verbal fluency, verbal memory and visual-motor processing are observable. These cognitive defects remain stable in the chronic phase of schizophrenia. On the other hand, cognitive dysfunctions in bipolar disorder patients have a heterogeneous pattern. One group of patients show no evidence of cognitive dysfunction while one group has limited dysfunction (of processing speed, attention, verbal learning and social cognition) and another one has wide spread dysfunctions as seen in schizophrenia. Despite its importance, no satisfactory results have been achieved in the treatment of cognitive dysfunctions in schizophrenia and bipolar disorder. In this article, the evaluation and treatment of the most frequent cognitive dysfunctions of schizophrenia and bipolar disorder are reviewed.
Keywords: Schizophrenia, bipolar disorder, cognitive dysfunction, cognitive evaluation, cognitive remediation

ÖZ

Bilişsel bozukluklar hem şizofreni hem de bipolar bozukluk seyrinde iyileşme ile en yakından etkili hastalık bileşenidir. Bilişsel işlevlerdeki bozulma hem bir endofenotip özelliği göstermekte hem de tedavi sürecine bağlı olarak da ortaya çıkabilmektedir. Şizofrenide ilk ataktan başlayarak bilişsel esneklik, baskılama, sözel akıcılık, sözel bellek ve görsel-motor işleme alanlarında bozulmalar gözlenmekte ve kronik hastalık evresinde bu bulgular değişmemektedir. Öte yandan bipolar bozukluk hastaları ise bilişsel işlevler yönünden birbirinden çok farklı özellikler göstermektedir. Bir grup hastada hiçbir bilişsel bozukluk saptanmazken; diğer bir grupta sınırlı alanlarda (işlem hızı, dikkat, sözel öğrenme ve sosyal biliş) bozukluk gözlenmekte; üçüncü bir grupta ise şizofrenidekine benzer yaygın ve ağır bilişsel bozukluklar izlenmektedir. Bu hastalıklarda oynadığı önemli role karşın bilişsel işlevlerin tedavisinde ne yazık ki istenilen sonuçlara ulaşılamamıştır. Bu gözden geçirme yazısında şizofreni ve bipolar bozuklukta görülen bilişsel işlev bozuklukları ve bunların tanınmasına yönelik testler, bilişsel rehabilitasyon için yapılabilecekler ve henüz gelişme aşamasındaki bilişsel işlev farmakoterapisine yer verilecektir.
Anahtar sözcükler: Şizofreni, bipolar bozukluk, bilişsel işlev bozukluğu, bilişsel onarım, bilişsel değerlendirme

Introduction

In the waning days of the 19th century, Kraepelin, who published the 6th edition of his book titled 'Psychiatrie,' differentiated schizophrenia, known as 'dementia praecox" at the time, from manic-depressive illness (bipolar disorder). During the course of schizophrenia, cognitive deterioration was observed, whereas, in manic-depressive illness, such deterioration was not evident, a distinction that Kraepelin took into account (Sedler 1994). Throughout the 20th century, Kraepelin's introduced dichotomous approach retained its validity; however, studies conducted as the century drew to a close demonstrated the presence of cognitive impairment not only in schizophrenia but also in bipolar disorder (Douglas et al. 2018, Li et al. 2020). Moreover, cognitive dysfunction has been found to be the disease component that has the most significant impact on the course of the disease and quality of life in both schizophrenia and bipolar disorder (Green 2006).

While evidence of cognitive impairment in schizophrenia is visibly apparent, cognitive impairments observed in bipolar disorder have been attributed to attention and motivation deficits during manic episodes. Recent studies, however indicate that the cognitive impairment observed in bipolar disorder is also present in the

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baseline and euthymic periods of the disorder (Douglas et al. 2018, Eker and Altinbaş 2020). Additionally, the question of whether a similar deterioration to that seen in schizophrenia is present in bipolar disorder remains a subject of debate. It is posited that the early-onset and psychotic subtype of bipolar disorder also display cognitive impairments prior to the onset of the disorder (Eker & Altinbaş 2020). Following an overview of cognitive impairments observed in schizophrenia and bipolar disorder and their assessment, this review will deliberate on potential treatment approaches."

Cognitive Impairments in Schizophrenia

Cognitive impairments, difficulties in impulse control, and mood symptoms are observed in addition to positive and negative symptoms that constitute the diagnostic criteria for schizophrenia (APA 2013). Cognitive impairments identified in schizophrenia often manifest independently of the illness's diagnostic criteria. Cognitive deficits in schizophrenia patients have been associated with responses to pharmacotherapy and psychotherapy, relationship stability, continuity in occupational functioning, and overall lifespan. The most prevalent cognitive impairments in schizophrenia encompass deficits in attention, working memory, processing speed, episodic learning and memory for verbal and nonverbal information, executive functions, reasoning, and problem-solving skills. The decrement in these skills is generally within the range of 0.5 to 0.75 standard deviations below the population norm. It should also be noted that approximately 30% of the general population exhibits abilities in these domains at 0.5 standard deviations or below (Husain and Schott 2016).

When evaluating the pre-illness states of schizophrenia patients, it is evident that cognitive impairments that commence in childhood intensify during adolescence and immediately before the onset of the disorder. During the chronic phase of the illness, there appears to be no significant alteration in the prevalence and frequency of neurocognitive symptoms. The pre-illness functional status of patients also influences their social and cognitive functioning (Woodberry et al. 2008, Menkes et al. 2019).

Particular deficiencies in executive functions and problem-solving skills mark the disorder's early stages during adolescence. This observation has suggested that an underlying neurodevelopmental disorder is at the root of this condition. Healthy individuals typically experience an increase in their vocabulary as they age. Conversely, schizophrenia patients exhibit a deterioration in their speech, a phenomenon that aligns with the hypothesis of accelerated aging in schizophrenia. Starting from the initial episode of the illness, impairments in cognitive flexibility, inhibition, verbal fluency, verbal memory, and visual-motor processing are evident and remain consistent throughout the chronic phase of the disease. Additionally, while deficits in visual analysis and organization are less frequent in early-onset patients, these impairments become more prevalent in the later stages of the illness (Tschentscher et al. 2023).

Further evidence indicating the endophenotypic characteristics of cognitive impairments observed in schizophrenia comes from studies involving healthy relatives of patients. However, it is vital to acknowledge the possibility that these data could also pertain to individuals who are currently healthy but might develop the illness later (Agnew-Blais and Seidman 2013). Numerous studies have demonstrated the hereditary transmission of cognitive impairments, and comprehensive reviews and meta-analyses have been published in this domain (Sitskoorn et al. 2004, Agnew-Blais and Seidman 2013). Similar to schizophrenia patients, healthy relatives also display poorer performance in verbal memory and Trail Making Test - Part B compared to healthy controls (Sitskoorn et al. 2004). However, no cognitive test sufficiently distinguishes healthy relatives from healthy controls, with effect sizes indicating a 65% overlap. This overlap suggests that a considerable portion of healthy relatives possess normal cognitive functions.

The medications used in the treatment of cognitive impairments inherent to the nature of the illness also contribute to the observed deficits. Notably, the effects of first-generation antipsychotic drugs and clozapine have been evaluated negatively. In contrast, the dosage of clozapine remains uncertain, and it should be selected for patients exhibiting treatment-resistant conditions with poorer performance (Baldez et al. 2021). The European Psychiatric Association recommends avoiding first-generation antipsychotic drugs to mitigate cognitive side effects (Vita et al. 2022).

In summary, neurocognitive assessments conducted following the initial phase of the disorder have revealed that these patients possess cognitive impairments not markedly distinct from those of chronic patients (Hoff et al. 1999, Mesholam-Gately et al. 2009). Considering the frequent occurrence of cognitive impairments in healthy relatives, it would be appropriate to conceive schizophrenia as a neurodevelopmental disorder, giving rise to widespread cognitive deficits (Rapoport et al. 2012).

Cognitive Impairments in Bipolar Disorder

While bipolar disorder primarily manifests with mood symptoms, cognitive impairment is also frequently observed. Initial investigations into cognitive impairments in bipolar disorder were initially linked to attention and/or motivation deficits observed during manic episodes (Bulbena and Berrios 1993). Subsequent studies, however, have indicated that neurocognitive impairments are associated with the chronic and prolonged course of the illness, and furthermore, these impairments persist even during euthymic periods. It has been observed that being in a euthymic state does not compensate for deficits in verbal memory and executive functions (McKay et al. 1995, van Gorp et al. 1998). In fact, it is now well-established that verbal memory and executive function deficits are the most commonly encountered neuropsychological impairments in bipolar disorder (Cotrena et al. 2020). Examination of healthy relatives presumed to carry endophenotypes of individuals with bipolar disorder has revealed that while not as severe as patients, they exhibit poorer performance than healthy controls in verbal memory, executive functions, and social cognition domains (Bora et al. 2009, Bora and Özerdem 2017).

Individuals with bipolar disorder exhibit cognitive impairment in varying frequency and domains. While some patients do not exhibit any cognitive impairment, others display deficits in specific areas (processing speed, attention, verbal learning, and social cognition), and a third group exhibits widespread and severe cognitive impairments akin to those seen in schizophrenia (Burdick et al. 2014). It has also been demonstrated that periods of exacerbation with psychotic symptoms and severe manic episodes are associated with worse cognitive functioning (Bora 2018). Additionally, the group of bipolar disorder patients without cognitive impairment was found to have better social cognition than the healthy control group.

In summary, it is postulated that certain individuals with bipolar disorder demonstrate poorer neuropsychological test performance due to neurodevelopmental or neurodegenerative processes, forming a subgroup within the disorder characterized by early onset, frequent relapses, and psychotic symptoms (Bora 2016, Kloiber et al. 2020). Conversely, the lack of overall cognitive deterioration in longitudinal follow-up of other patients supports this notion (Bora and Özerdem 2017). When interpreting neuropsychological test results, alongside this heterogeneity, one should also bear in mind the potential influence of medication side effects, sleep disturbances, and subthreshold symptoms frequently experienced by patients.

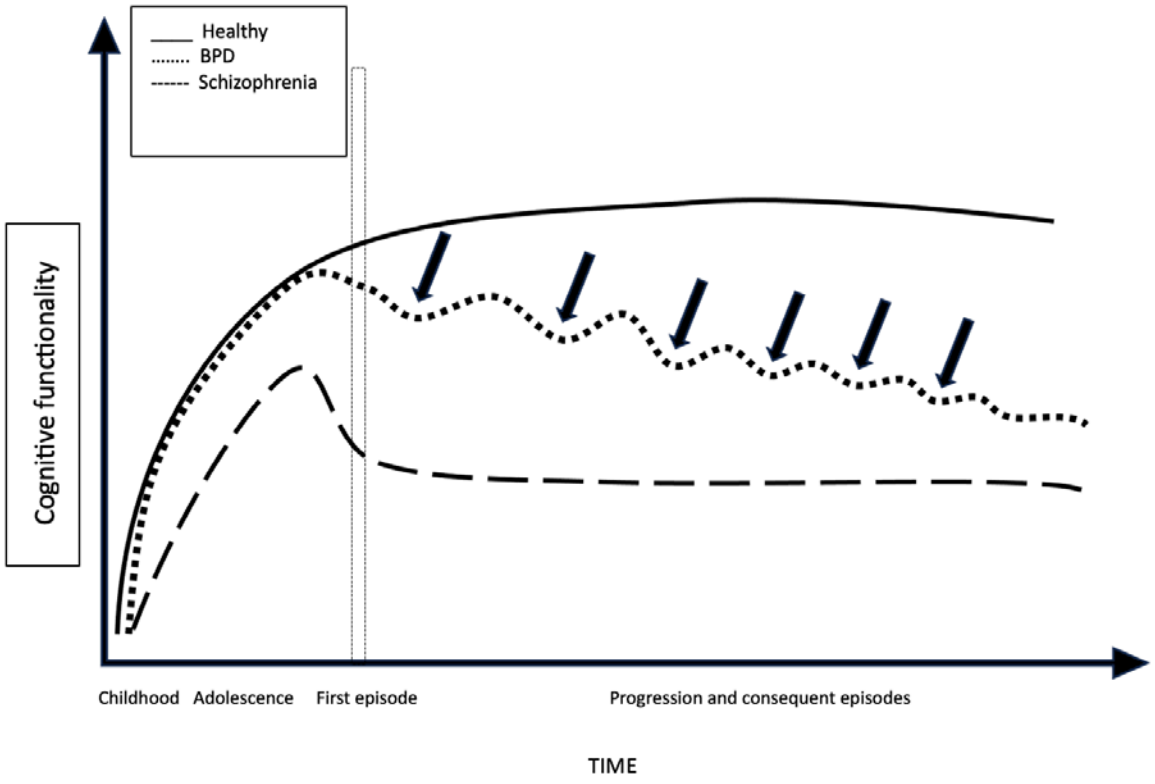

Figure 1. Comparison of cognitive functioning level of healthy people with patients with bipolar disorder and schizophrenia. (Lewandowski et al. 2011)

Recognition and Assessment of Cognitive Disorders:

The fact that psychiatric diagnostic systems are not based on laboratory findings and the interpretation of many symptoms is left to the clinician causes challenges in diagnosis and treatment. On the other hand, as in many areas of medicine, setting measurable characteristics and targets for both diagnosis and treatment is essential, albeit difficult, in psychiatric disorders. Researchers working in the field of cognitive disorders in schizophrenia have developed the MATRICS (Measurement and Treatment Research for Improving Cognition in Schizophrenia) project for this purpose. The MATRICS project was recognized by the FDA (US Food and Drug Administration) and the EMEA (European Medicines Agency). The agreed test battery (MATRICS consensus cognitive battery, MCCB) includes standardized, performance-based cognitive assessments (Table-1). Apart from MATRICS, CNTRICS (Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia) and CNTRACS (Cognitive Neuroscience Test Reliability and Clinical Applications for Schizophrenia) have also made recommendations for research on cognitive functions in schizophrenia (MacQueen and Memedovich 2017).

Table 1. MATRICS Consensus Cognitive Battery (MCCB)
Processing speed
Categorical fluency Brief Assessment of Cognition in Schizophrenia (BACS)-Symbol Coding Trail making test A
Attention/Vigilance
Continuous Performance Test-Identical Pairs (CPT-IP)
Working memory
Verbal: University of Maryland Letter-Number Span Non-verbal: Weschler Memory Scale -III (WMS-III Spatial Span) - Spatial Span
Verbal learning
Hopkins Verbal Learning Test (HVLT) -revised
Visual learning
Brief Visuospatial Memory Test (BVMT) - revised
Reasoning and problem solving
Neuropsychological Assessment Battery (NAB) -Labyrinths
Social cognition
Meyer-Solovay-Caruso Emotional Intelligence Test

Bipolar disorder is an illness characterized by prominent emotional fluctuations. The emotional burden of stimuli is more significant than schizophrenia and affects cognitive functions. Consequently, there is a need for cognitive function assessments in bipolar disorder that also consider emotional significance. Therefore, there are warnings against employing methods used in schizophrenia research to investigate cognitive impairments in bipolar disorder (MacQueen and Memedovich 2017, Tschentscher et al. 2023). For this purpose, the Brief Assessment of Cognition in Affective Disorders (BAC-A) has been developed (Table 2). On the other hand, there are researchers who also find the recommendations of MATRICS, CNTRICS, and CNTRACS to be adequate (MacQueen and Memedovich 2017).

Table 2. Brief Assessment of Cognition in Affective Disorders (BAC-A)
Basic Brief Cognitive Assessment
Verbal Memory
List Learning
Working Memory
Digit Sequencing Task
Motor Speed
Token Motor Task
Semantic Fluency
Verbal Fluency, Categorical
Executive Functions
Tower Of London Test
Attention and Motor Speed
Symbol Coding
Emotional Tests
Emotional Suppression
Emotional Stroop
Affective Processing Test

Treatment of Cognitive Impairments

Non-Pharmacological Approaches

Restoring functionality and improving quality of life are the primary objectives in all mental disorders. However, achieving this goal, especially in cases of schizophrenia, often proves to be challenging. Recent research suggests that individuals with bipolar disorder also face similar difficulties (Burdick et al. 2014). While cognitive impairments are crucial factors influencing functionality and quality of life in schizophrenia and bipolar disorder, there is currently no biological treatment that can fully rectify these impairments (Bowie et al. 2020).

Cognitive Remediation Therapies (CRT) have emerged as a non-pharmacological intervention. CRT encompasses a range of therapeutic interventions involving behavioral exercises that aid in various aspects of recovery. CRT aims to enhance functional recovery by applying scientific learning principles, with the goal of addressing cognitive impairments through behavioral training. It is most effective when implemented in a context that supports daily functioning and provides opportunities to practice learned skills. The main cognitive domains targeted by CRT should include attention, memory, executive functions, social cognition, and metacognition (Bowie et al. 2020).

The effectiveness of cognitive remediation therapies in schizophrenia is often limited when used in isolation. Studies have shown that combining CRT with other psychiatric rehabilitation methods, such as social skills training, occupational therapy, or workplace support, leads to greater effectiveness. While research assessing treatment outcomes demonstrates modest improvements in cognitive functions, the impact on functionality tends to be more substantial (Wykes et al. 2011).

Maintaining engagement in rehabilitation programs is a significant challenge. To sustain motivation, these programs should be designed to be practical, enjoyable, and interactive, thus promoting patient participation and continuity. Considering the social challenges faced by individuals with schizophrenia, a group setting might be more beneficial for certain patients. Moreover, it is important to recognize that the expectations of individuals with bipolar disorder to return to a "normal" state are partially realistic and that support at every step is crucial (Wykes et al. 2011, Bowie et al. 2020).

Pharmacotherapy

The concept of neuroleptics, which induce emotional, mental, and motor dullness, serves as the basis for their effects. First-generation antipsychotics align with this classic neuroleptic characterization. However, the neuroleptic effects of second-generation antipsychotics, which are more commonly used, are subject to debate. Second-generation antipsychotics are believed to have more favorable effects on negative symptoms and cognitive functions. For example, the use of lurasidone as an adjunctive treatment in euthymic patients with bipolar disorder has been shown to have positive effects on cognitive functions (Yatham et al. 2017).

While clozapine's impact on social functioning is clear, it's important to consider the potential relation between its anticholinergic side effects and cognitive impairments (Kapczinski et al. 2021, Joshi et al. 2021). In fact, reduced binding to muscarinic receptor-1 (M1) in the hippocampi of schizophrenia patients has already been demonstrated, suggesting potential negative effects on learning (Bakker et al. 2020).

Antipsychotics that modulate serotonin (5-HT) and dopamine (D) receptors are believed to aid cognitive functions due to their partial agonist effects on both receptor types. Cariprazine, which is more effective on dopamine receptor-3 (D3) than dopamine receptor-2 (D2), and brexpiprazole, which has stronger effects on D2 than D3, both with partial 5-HT1A agonist effects, are believed to be associated with improvements in negative symptoms and cognitive functions. Brilaroxazine is thought to impact positive and cognitive symptoms of schizophrenia through partial agonistic effects on D2, D3, D4, 5-HT1A, and 5-HT2A receptors (Lobo et al. 2022).

Newer antipsychotic drugs have been developed with more potent effects on the serotonin system than the dopamine system. It is anticipated that these newest-generation drugs may also affect cognitive symptoms. For example, roluperidone, an antagonist of 5-HT2A and sigma-2 receptors, is particularly associated with improvements in verbal memory (Lobo et al. 2022).

Lumateperone, which functions as a 5-HT2A antagonist and a presynaptic D2 agonist/post-synaptic D2 blocker, has also been proposed to improve negative symptoms of schizophrenia. With its serotonin 5-HT2A inverse agonist effect, pimavanserin is another antipsychotic believed to impact cognitive processes (Lobo et al. 2022).

Ulotaront, an agonist of the trace amine-associated receptor-1 (TAAR-1), has been described by the FDA as a groundbreaking treatment due to its unique antipsychotic effects. Apart from alleviating core symptoms of schizophrenia, it has been observed to positively impact cognitive functions (Koblan et al. 2020). However, more evidence is needed for these treatments.

It is known that N-methyl-D-aspartate type (NMDA) glutamate receptors play a role in both the core symptoms and cognitive impairments of schizophrenia (Veselinović and Neuner 2022). Glutamate precursors such as N-acetyl cysteine (NAC) are being investigated for their neuroprotective effects and impact on cognitive symptoms of schizophrenia. Alpha-lipoic acid, omega-3 fatty acids, nitric oxide, and NAC have shown positive effects on cognitive functions in schizophrenia, often based on animal studies (Vasconcelos et al. 2015, Pitsikas 2015, Pawełczyk et al. 2018).

Data also exists suggesting that due to estrogen's neuroprotective effects, it benefits the cognitive functions of schizophrenia patients. When estrogen is added to antipsychotic treatment, positive effects on metaphorical speech and concrete thinking have been observed (Bergemann et al. 2008).

Conclusion

Cognitive impairments are commonly encountered in severe mental illnesses like schizophrenia and bipolar disorder. Factors such as premorbid functioning levels, patients' living environments, lifestyles, and rehabilitation opportunities also influence cognitive functions. Given that cognitive impairment heavily impacts the course of the illness and quality of life, it should be investigated in every patient. While there is no definitive solution yet to address cognitive impairments in these disorders, newly developed medications and Cognitive Remediation Therapies hold promise.

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