

LITERATURE REVIEW:

COGNITIVE DYSFUNCTION IN SCHIZOPHRENIA

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ABSTRACT

Schizophrenia is a mental disorder which includes: positive symptoms, negative symptoms, cognitive symptoms, affective symptoms and aggressive symptoms. Cognitive disorder is the most severe disorder compared to other symptoms of schizophrenia because it can interfere with daily functions, including memory function, attention function, problem solving function, speech function and social skills.

Keywords: Schizophrenia, Diagnosis, Cognitive Dysfunction

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INTRODUCTION

Schizophrenia (schizophrenia; read "skit-se-fri-nia") is one of the severe mental disorders that can affect the thoughts, feelings and behavior of individuals. Schizophrenia is part of a psychotic disorder which is mainly characterized by a loss of understanding of reality and a loss of insight [1].

Cognitive function in Schizophrenia is one of the most critical in determining the quality of life in individuals with Schizophrenia. Where this cognitive function has the potential to be more severe compared to other symptoms of Schizophrenia such as hallucinations, delusions, or even negative symptoms [2].

Schizophrenia patients experience memory loss and difficulty in recalling memory and language. a number of studies conclude that cognitive decline in men is more severe than in women for example in recalling memory and in recent studies there were no language, visuospatial and attention problems [3].

This literature review discusses cognitive dysfunction in Schizophrenia with the hope that it can provide a clear picture of cognitive dysfunction in Schizophrenia itself.

Cognitive

Cognitive is an important function in the brain that affects the skills in solving a problem, making decisions and creativity [4].

Cognitive Level

According to Piaget, there are 4 stages of cognitive development, namely [5]:

1. The Sensorimotor stage in the age range is around 0-2 years
2. Preoperational stage in the age range of about 2-7 years
3. Concrete operational stage in the age range of about 7-11 years
4. Formal operational stage in the age range of about 11 years and above

Cognitive Domain Division:

The Cognitive Function according to JR Hodges consists of 3 modalities:

1. Attention / concentration

2. Memory
3. Function intellectuals, behavior social and personality (higher-order intellectual behavior and personality)

Hecker mentions the cognitive domain consisting of 9 modalities:

1. Memory
2. Language
3. Praxis
4. Visuospatial
5. Attention and concentration
6. Calculation
7. Make decisions / Judgment and insight
8. Reasoning
9. Think abstract / abstract thinking

Factors That Affect Cognitive:

1. Age

The aging process encourages cognitive impairment due to structural and functional changes in the brain especially in the hippocampal region, showing a decrease in gene plasticity, reduced synaptic plasticity, decreased cognitive function and osteoporosis [6].

2. Intelligence Quotient (IQ)

Patients with low IQ have low cognitive function too [7].

3. Neurotransmitter

- a. Dopamine

Animal studies show prefrontal dysfunction in schizophrenia, and the D1 receptor in the brain region is thought to play an important role in various functions of the frontal lobe such as working memory [8].

- b. Serotonin

The availability of 5-HTT in the fronto-striatal area is associated with better performance in executive functions and logical reasoning [8].

- c. Norepinephrine

The central norepinephrine system plays an important role in arousal and concentration, and the norepinephrine transporter is a target in pharmacotherapy for depression and ADHD [8].

- d. Glutamate

Any deviation in the function of glutamatergic synapses, has the potential to interfere with the cognitive abilities of the human brain [9].
 - e. GABA

GABA concentration is related to cognitive function in the area of the frontal cortex [10].
 - f. Acetylcholine

Activation of the $\alpha 7$ acetylcholin receptor enhances cholinergic neurotransmission and the release of glutamate and dopamine which can exert a cognitive effect [11].
4. Neuropathology
 - a. Frontalis cortex

The main function of the frontal cortex is motor activation, intellectual, conceptual planning, aspects of personality, and aspects of language production.
 - b. Temporal Cortex

The main function of the temporal cortex is language, memory, and emotions. In the temporal lobe there is the hippocampus which is part of the limbic system and plays a role in the memory (memory) and visuospatial functions.
 - c. Parietal Cortex

The function of the parietal cortex is an association for visual, tactile, and auditory input.
 - d. Occipital Cortex

The occipital lobe is the main sensory cortex for visual input.
 5. Genetic

Cognitive function is inherited from parents. From research conducted by Davies et al., Showed genome significant relationships in 3 genomic regions, namely 6q16.1 (MIR2113), 14q12 (AKAP6 / NPAS3 region) and 19q13.32 (TOMM40 / APOE region) and HMGN1 located at chromosome 21. Gen 19q13.32 has long been associated with dementia and has recently been linked to non pathological cognitive aging. While genes 6q16.1, 14q12, and HMGN1 are associated with brain development, neurological function, psychiatric disorders, and educational attainment [12].

Cognitive Dysfunction in Schizophrenia

Neurocognitive deficits in schizophrenia occur mostly due to problems in neurological development that continue and increase the risk of psychosis. The severity of cognitive deficits varies between individuals, due to the heterogeneity of each individual's own neurobiological conditions. In individuals who have severe cognitive dysfunction at an early age, will result in more severe neurodevelopmental disorders. Synaptic connectivity tends to be abnormal even in individuals with schizophrenia who have no symptoms of cognitive decline. In a study conducted by Reichenberg and Harvey, there was a disruption in memory and executive control processes that occur in Schizophrenia patients, the amount of which is stable and the same throughout the world.

In the opinion of Kar and Jain, the major cognitive domains affected in Schizophrenia include [4]:

1. Attention and vigilance

In Schizophrenia, attention disorder is a major cognitive deficit disorder. Decrease in speed in interpreting information quickly is part of attention problems in schizophrenia.
2. Learning and memory

In Schizophrenia there is also a disruption of emotional modulation from memory and attention, which initially takes longer to interpret information than normal people, and performs better with repeated exposure. Schizophrenia shows good recognition memory and shows more severe impairment in explicit memory than implicit memory.
3. Working memory

Working memory disorders are at the core of Schizophrenia's cognitive deficits, which are related to the clinical picture and functional consequences of Schizophrenia. Both verbal and non-verbal working memory are dysfunctional in schizophrenia. Working memory plays an important role throughout the meaningful process. Abnormalities in strategy and working memory contribute to verbal encoding deficits and other cognitive functions in Schizophrenia.

4. Executive Function

Schizophrenic patients experience executive function deficits that cause disturbances in the treatment of appropriate response response to situations and activities that aim directly

5. Speed in receiving and processing information

In interpreting a task, there is a severe deficit in Schizophrenia patients.

6. Problem solving

Schizophrenia patients who experience interference with executive function, will have difficulty in adapting to the rapid changes in their surroundings. Poor problem solving in Schizophrenia can be due to cognitive deficits or is due to secondary deficits in the main areas of cognition in the initiation of tasks, attention, concentration, and working memory, the main deficits of executive functions such as difficulty in shifting tasks (due to impaired ability to think alternative), repetition of errors (perseveration), and a decrease in average processing speed which will prolong the resolution of problems [14].

7. Social cognition

Social cognition such as recognizing and distinguishing faces and emotions becomes a disorder for Schizophrenia patients who significantly interferes with social work life. Cortical inhibition disorders play a role in the social cognition of schizophrenic patients. Schizophrenia patients experience a large decrease in general intellectual abilities in neuropsychological assessment. Deterioration of intellectual function is not only caused by deterioration in IQ, but is more related to a decrease in specific cognitive domains such as attention, processing speed, and working memory [15].

Neurobiology of Cognitive Deficits in Schizophrenia

In Schizophrenia, brain development abnormalities begin early in prenatal life, which increases during childhood and continues into adulthood. the process of neurogenesis continues into adulthood until the end of life, although the process is limited to certain brain areas such

as the olfactorius bulb, hippocampus, and periventricular regions. Schizophrenia is believed to occur due to interference with abnormal nerve development. Abnormalities in nerve development may be responsible for the occurrence of cognitive deficits in Schizophrenia.

Abnormalities in Schizophrenia are found in many areas of the brain; the brain most consistently changes in parts such as the prefrontal cortical region, inferior parietal lobules, amygdala, superior temporal gyrus, medial temporal lobe, basal ganglia, thalamus, corpus callosum and cerebellum.

Brain changes can be explained as a cumulative effect of neurodevelopmental disorders, changes in neuroplasticity and changes in neuron maturation. Core symptoms of Schizophrenia such as negative symptoms and executive dysfunction that take place as a result of changes in neuroplasticity. Brain-derived neurotropic factors (BDNF) are associated with hippocampal neuroplasticity, which is involved in cognitive processing. Schizophrenia causes changes in nerve development, which alter BDNF mediated hippocampal neuroplasticity, associated with cognitive deficits.

Cognition is also strongly influenced by genetic factors. Among various cognitive domains, genetic factors affect working memory and intelligence. Interactions between genes and the environment affect brain development and cognition. So it can be concluded that the memory deficit that occurs in people with Schizophrenia can be explained as the influence of genetic factors [16].

Disorders of the schizophrenia 1 / Disrupted gene in Schizophrenia 1 (DISC1) associated with schizophrenia also affect neuroplasticity. The gene, DISC1 regulates the process of neuritic growth, expansion and migration in brain development. Neuregulin 1 (NRG 1) is a candidate gene, which is involved in the development of schizophrenia which has a role in regulating synaptic plasticity. This gene can be associated with cognitive deficits due to abnormal neuroplasticity.

The gene "Akt1 (Serine / threonine specific protein kinase)" has also been found to play an important role in neuronogenesis in the hippocampus. Phosphorylated Akt levels are found to be lower in individuals with Schizophrenia. A gene called the human dystrobrevin protein binding gene / Dystrobrevin Binding Protein 1 (DTNBP1) is also linked to Schizophrenia and is known to determine cognitive abilities in general. A single nucleotide polymorphism in the DTNBP1 gene influences cognitive

abilities in individuals with Schizophrenia. A study of genome-wide associations in the Irish population revealed an association of the ZNF804A (Zinc Finger Protein 804A) gene with Schizophrenia. It is known to modulate dorsolateral prefrontal cortex coupling with the hippocampus and maintain binding sites for several neurotropic factors. In another study revealed the involvement of ITIH3 / 4 (Inter alpha trypsin H3 / 4 heavy chain inhibitor), CACNA1C gene (Calcium channel, voltage-dependent, L type, alpha 1C) and SDCCAG8 (Serologically Defined Colon Cancer Antigen) in Schizophrenia, involved in modulation of various neuro-circuits and tend to influence cognition [17].

In a recent study it was revealed that the M6a neuron glycoprotein (N6 Methyladenosin) has a role in facilitating neurite growth, synaptogenesis, and neuroplasticity. In individuals with Schizophrenia, irregularities in the brain are found, which results in the disconnectivity of deviant connections in the brain resulting from abnormal synaptic plasticity that causes disconnectivity to brain neuron tissue. Disconnectivity due to abnormal synaptic plasticity, results in disruption of learning and information processing, which is manifested in the form of Schizophrenia cognitive deficits. Some important neuromodulatory neurotransmitters such as dopamine, acetylcholine, and serotonin play a major role in abnormal synaptic plasticity. Memory disorders are well reported in Schizophrenia. The degree of damage has little to do with the duration of the disease, the severity of the psychopathology, the treatment used and the age of the patient. One memory deficit that works is one of them is a core cognitive deficit in Schizophrenia. Working memory deficits are associated with certain dysfunctions of brain areas such as the left dorsolateral prefrontal cortex, medial prefrontal cortex and visual cortex. Imbalance in dopaminergic, glutamatergic, and gamma-aminobutyric acid activity (GABA) in the functional brain area above is responsible for memory deficits acting on Schizophrenia [18]. Working memory deficits are associated with certain dysfunctions of brain areas such as the left dorsolateral prefrontal cortex, medial prefrontal cortex and visual cortex. Imbalances in dopaminergic, glutamatergic, and gamma-aminobutyric acid activity (GABA) in the functional brain area above are responsible for memory deficits acting on Schizophrenia [18]. Working memory deficits are associated with certain dysfunctions of brain areas such as the left dorsolateral prefrontal cortex, medial

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Impact / Effect of Cognitive Dysfunction and Hallucinations

Hallucinations are false sensory perceptions that are not accompanied by real external stimuli, there may or may not be misinterpretations of hallucinatory experiences [1].

Hallucinations occur in patients with Schizophrenia as much as 60-70%, generally are auditory hallucinations although it does not rule out the existence of other types of hallucinations such as hallucinations: visual, somatosensory, olfactory and gustatory. These hallucinations generally contain negative contents with coarse language with frequent frequency, thus interfering with the daily activities of the patient. These hallucinatory experiences, usually considered by sufferers to be from outside [19].

From several studies concluded that hallucinations occur because of:

1. The role of intrusion and cognitive impairment.
2. Influenced by top-down perception factors (perception influenced by internal experience or no external stimulation).
3. One's inability to distinguish between shadows and reality, between perceptions of internal and external experience [19].

Symptoms of Apathy in Schizophrenia

Apathy or lack of will (also called avolition or abulia) refers to the greatly reduced role of a person in daily activities and the lack of initiative accompanied by ignorance. Apathy is the strongest predictor of deterioration in clinical practice.

Networks in the frontal and striatal medial regions have a very important role in motivated behavior in healthy people. Disturbances in these components - or connections between - tissues are strongly associated with apathetic brain disorders. The dorsal anterior cingulate cortex (dACC) includes the anterior cingulate sulcus (Brodmann area 24c & 32). Here the medial prefrontal cortex refers to the

prefrontal and ventromedial orbitofrontal cortex, two anatomically overlapping areas (specifically Brodmann areas 10, 11 and 47) [20].

The cognitive techniques used in this approach aim to modify this dysfunctional belief. Where, this intervention improves functional outcomes but does not have a significant effect on anhedonia. Alternative psychological interventions are used to maximize positive emotions. The field of affective science has described emotional regulation strategies that increase the frequency, intensity, and duration of positive emotional experiences. These strategies include anticipating or remembering pleasure, expressing emotions through non-verbal behavior, directing controlled attention toward positive experiences when disturbances occur and sharing positive experiences with others. They tend to avoid interpersonal interactions and anticipate lower amounts of pleasure in those interactions [19].

Using a newly developed technique to estimate three-dimensional subcortical structure shapes, researchers found that apathetic individuals have greater atrophy in NAc and dorsolateral caudate heads, with the strongest results in left NAc [21].

Patterns of social cognitive impairment

Schizophrenia is associated with disturbances in facial perception, mental regulation and emotions, but they can still remember emotions they have experienced. However, it is very difficult to draw firm conclusions because there is very little literature on this subject. Research on social cognitive decline in schizophrenia patients in Indonesia, especially in men, has a significant relationship with antipsychotic administration. Therefore, anti-psychotic drugs need to be further investigated regarding the relationship between sexual function in individuals with schizophrenia.

Individuals with Schizophrenia experience a decline in social cognitive processes in 4 aspects, namely (perception of social cues, sharing of experiences and mentalization) and intrapersonal processes (experience and regulation of emotions). By using this classification system, it can be seen that in individuals with Schizophrenia, they experience a social cognitive decline in both interpersonal and intrapersonal dimensions. Social cognition can be divided into reflective and reflexive social processes, where individuals with schizophrenia

experience a decrease in their reflective and reflexive functions. The reflective process means that individuals with schizophrenia require a great effort to process the information received. Whereas the reflexive process is related to a desire to share emotional experiences.

Likewise, a process of mentalization in individuals with Schizophrenia requires more skills in considering the perspectives of others and this is very dependent on the perception of social cues received by the individual. One important example of integration between social processing systems is empathy.

Reduced self-ownership (Insight)

The absence of sight (awareness of pain) is part of psychosis. Can be divided into three:

1. Realized he was sick
2. Recognize psychotic symptoms as abnormal
3. Receive treatment

Poor surveillance will result in non-compliance with treatment, poor individual functioning in daily activities, severe psychopathology, recurrence and low cure rates. This is not only bad for the patient himself but also causes distress for his family, friends and clinicians who handle it. The cognitive and neural basis of self-view in people with psychosis is not yet clear and remains a mystery. Even so, some researchers believe that there is a close relationship between self-view and a reduction in cognitive function, which is believed to be due to a significant change in the prefrontal cortex. It was stated in a meta-analysis that there is a relationship between self-insight, some cognitive aspects of self-knowledge and neurocognition. Where this shows the complexity of the self-view which is influenced by neurocognitive and cognitive impairment is one of the factors that contribute to the formation of this self-view [22].

Neurocognitive damage that occurs together with reduced self-esteem (both social cognition, emotional and mental recognition) only occurs in patients who experience multiple episodes or chronic psychosis. In other words, cognitive impairment does not occur in patients who have psychosis for the first time [23].

An insight into psychosis is hypothesized as a self-evaluation called Epstein's Cognitive Experimental Self Theory (CEST). Based on CEST, there are two human

responses to the world, namely rationality and experience. Where these two things can distinguish adaptive mental systems or not. Rational systems operate the conscious realm of memory and language. While experience (experiential) operates the subconscious and processes information quickly and thoroughly. Rational systems work slower and require more effort than experiential systems. Even though both systems work independently, they interact and influence one another [24].

Some hypotheses state that the reduced insight is due to abnormalities in the brain circuits that serve self-evaluation. Self-evaluation is a person's ability to think and make decisions that involve cognitive, personality, physical and emotion. Another study mentioned the involvement of the prefrontal medial cortex and posterior cingulate in this self-evaluation process. These lesions are in line with the alertness disorder experienced by the patient [19].

Increased self-esteem is closely related to good response between the inferior frontal gyrus, anterior insula and inferior parietal lobe. In addition to this, activation of the ventromedial prefrontal cortex is also found during self-reflection [25].

SUMMARY

Cognitive dysfunction is influenced by a number of factors where development in early life affects later schizophrenia. It is also influenced by changes in neurodevelopment that change the mediation of BDNF hippocampal neuroplasticity, genetic factors involving DISC1, Akt 1, and M6a Neuron glycoprotein. Where the dysfunction of these factors will result in hallucinations, apathy symptoms, social dysfunction and reduced self-control.

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