

# EMOTIONAL PROCESSING IN SCHIZOPHRENIA

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## Abstract

Schizophrenia is a severe psychiatric disorder characterized by positive, negative, and cognitive symptoms. One of its main features is a deficit in emotional and social cognition. Patients often fail to adequately detect and interpret emotional stimuli, which contributes to impaired functioning. Functional MRI studies have revealed reduced activation in the medial prefrontal cortex, amygdala, and insula, which are centers to social cognition. Hyperactivity in the amygdala and prefrontal areas is associated with auditory verbal hallucinations containing emotional content. Molecular explanations for the disrupted neurotransmission include changes in brain pH that primarily affect NMDA receptor function, noradrenergic signaling, and synaptic plasticity. A genetic risk factor for schizophrenia is altered miR-137 expression, which contributes to abnormal prefrontal activation during emotional processing. These findings highlight the complexity of emotional symptoms in patients diagnosed with schizophrenia.

**KEYWORDS:** auditory verbal hallucinations, dopamine, emotional processing, miR-137, schizophrenia

## INTRODUCTION

Schizophrenia is a psychiatric disorder that greatly reduces the quality of life, and is a leading cause of human disability, affecting 0.7–1% of the world's population, although it appears with a higher rate in men compared to women.<sup>1,2</sup> The pathological symptoms in schizophrenia are subdivided into positive, negative, and cognitive.<sup>3</sup> Positive symptoms include hallucinations, delusions, and disorganized speech. Negative symptoms include blunted affect, avolition, asociality, and anhedonia.<sup>4</sup> Symptoms must be present for at least six months and be severe for at least one month to make a diagnosis.<sup>4</sup> One of the main traits of schizophrenia is an overall deficit in social cognition, including social-emotional processing.<sup>5</sup> Patients diagnosed with schizophrenia find it hard to express their own feelings and do not completely understand the emotional expression of others. On the other hand, even though patients with schizophrenia show very few emotions externally, which is known as flat affect, they will strongly experience emotions inside if emotional stimuli are present.<sup>6</sup> This is a consequence of abnormal functional brain connectivity, hypo- or hyperconnectivity among the social brain regions.<sup>7</sup> This paper will focus on the mechanisms of difficulties in detecting and processing emotions in people diagnosed with schizophrenia.

### IMPAIRED EMOTION-DETECTION ABILITY IN SCHIZOPHRENIA-DIAGNOSED PATIENTS

The deficit of social cognition is one of schizophrenia's features, especially emotion perception and processing.<sup>8</sup> Emotion recognition is further impaired during episodes of positive symptoms when patients are unable to detect even the most basic emotions.<sup>9</sup> The parts of the brain responsible

for social functioning are the medial prefrontal cortex (PFC), the posterior superior temporal sulcus, the inferior frontal gyrus, the interparietal sulcus, the amygdala, the anterior and posterior cingulate cortex and the anterior insula. Activation in these areas is reduced in patients diagnosed with schizophrenia, and it is associated with worse functional outcomes.<sup>8</sup> Elsherif et al. observed that patients with schizophrenia show an impaired ability to spontaneously fixate on the eyes. In this study, eye fixation was indirectly measured using Signal Detection Theory (SDT) rather than eye-tracking. Participants were shown neutral, happy or sad masked faces with either eyes or a mouth visible and had to determine the presence of the feature, but not the emotional expression. SDT was used to calculate the discriminability index, which demonstrates perceptual sensitivity to facial features, and criterion bias, assessing decision-making tendencies. Fearful eyes were detected more accurately than neutral or happy eyes, while emotion recognition through the mouth was less accurate, with smiling mouths slightly easier to detect than fearful ones. These findings highlight that proper eye fixation is crucial for detecting emotional expressions, especially fearful ones.<sup>10</sup> It was concluded that, for people with schizophrenia, the recognition of emotions is particularly difficult if only the region around the mouth is used, and it is somewhat easier if only the eye region is used, because the visual features are more pronounced. Thus, the reduced activation of specific brain parts responsible for social functioning leads to difficulties in detecting and processing other people's emotions, which impairs the quality of life in patients with schizophrenia.

### EMOTION PROCESSING AND HALLUCINATIONS

The most common type of hallucinations are auditory verbal

hallucinations (AVH) which can be with or without emotional content,<sup>11</sup> while the emotional content is predominantly negative.<sup>12</sup> The likely reason why some AVHs have emotional content and others do not is an increased activity of the amygdala and the right ventromedial and dorsomedial prefrontal cortex (vmPFC/dmPFC). Increased resting-state cerebral perfusion has been observed in these areas in individuals with AVH with emotional content compared to patients with AVH without emotional content. This hyperperfusion in the amygdala is suggested to critically contribute to the emotional content of AVH, while the vmPFC/dmPFC hyperperfusion may indicate an insufficient regulation of this amygdala activity in patients with schizophrenia.<sup>11</sup> AVH with negative emotional content might be a consequence of the activation of the right hemisphere in Broca's area, which is associated with the production of swear words.<sup>12</sup>

### fMRI OF EMOTIONAL PROCESSING

Although resting-state fMRI studies are most commonly used for the examination of brain connectivity, Hyatt et al. used dynamic functional network connectivity (dFNC) because it allows us to see how brain connectivity patterns change during specific stimuli, not just during rest.<sup>13</sup> The emotions happiness and sadness are present in different brain organizational systems. In Hyatt's experiment, participants passively viewed videos of actors describing happy, sad, or neutral situations designed to simulate social-emotional interactions. Based on the results, four states are described. State-1 is the state when the video and audio materials were passively processed, State-2 is "sad-state" because it is activated when videos describing emotionally negative charged situations appeared, while State-3 and 4 are "happy-states" when happy circumstances are pictured. Happy and sad videos that present happy and sad emotional stimuli led to different activation patterns between individuals with and without schizophrenia. When watching happy videos, individuals with schizophrenia were unable to engage State-3, which is associated with happy emotions in individuals who have not been diagnosed with schizophrenia, and instead spent more time in State-4, which is the weakest connected state.<sup>13</sup> The fMRI tests confirmed the existence of a difference in emotion processing between healthy individuals and patients with schizophrenia.

### BRAIN CONNECTIVITY BEHIND EMOTIONAL PROCESSING IN SCHIZOPHRENIA

In people with schizophrenia, the main site of dopaminergic dysregulation is the nucleus accumbens (NAcc), which is part of the ventral striatum.<sup>14</sup> Individuals also exhibit an increased functional connectivity (FC) between the salience network (SN) and the right inferior and middle temporal gyrus (ITG and MTG).<sup>15</sup> The NAcc shows increased connectivity with the temporal lobes (including the inferior and fusiform gyrus) and reduced connectivity with the frontal cortex (including the superior frontal gyrus and anterior cingulate gyrus).<sup>14</sup> Emotional detection and processing in patients could be a consequence of an impaired division of task-positive regions (SN) and task-negative regions (ITG and MTG).<sup>15</sup>

The structures of temporal and frontal lobes are centers of language processing, while the frontal lobe and anterior cingulate gyrus are centers of cognitive control, and their altered connectivity could contribute to the impaired speech perception and cognitive deficits, which indirectly impact emotional processing.<sup>14</sup> Negative FC between the SN and left caudate has been linked to psychotic symptoms like hallucinations and delusions.<sup>15</sup> Changes in FC between the left NAcc and the left inferior temporal gyrus were negatively correlated with changes in positive symptom scores.<sup>14</sup> Significantly increased and positive FC between the SN and the right precentral gyrus is also detected.<sup>15</sup> The center for sensory and motor movement is the precentral gyrus. It is involved in the perception of facial expressions and emotions, which are part of social cognition. Among these areas, hyperconnectivity is observed and it could be associated with overactive information interaction, potentially leading to emotional and motional processing dysfunction.<sup>15</sup> It can be concluded that the greatest abnormal activity is present in the dopamine pathways in the nucleus accumbens, along with hyperconnectivity between the salience network, temporal and precentral regions in patients with schizophrenia. This is the neurobiological explanation for their errors in emotional processing, cognitive deficits, and psychotic symptoms such as hallucinations and delusions.

### PH CHANGES AND EMOTIONAL PROCESSING

A persistently low brain pH in schizophrenia leads to an imbalance in dopaminergic and glutamatergic transmission. One significant change is the alteration in NMDA receptor function. The half-maximum inhibition of these receptors occurs at a pH of 7.3, which is close to the physiological brain pH. A 0.2 pH unit decrease, as observed in schizophrenia, can substantially inhibit NMDA receptor activity, leading to increased glutamate release and inducing schizophrenia-like symptoms in individuals who are not diagnosed with schizophrenia, while worsening symptoms in people diagnosed with schizophrenia.<sup>16</sup> Low brain pH can affect chemosensitive noradrenergic neurons in the locus coeruleus (LC), which are responsive to changes in blood pH or partial pressure of carbon dioxide. Acidification can depolarize these LC neurons and increase their firing rates, causing a dopamine imbalance that is associated with positive and negative symptoms.<sup>16</sup>

### MOLECULAR BASIS OF EMOTIONAL PROCESSING IN SCHIZOPHRENIA

In the study by Pergola et al., RNA sequencing data from postmortem PFC was used to assess the expression of miR-137 target genes.<sup>17</sup> The microRNA miR-137, whose target genes are involved in working memory and emotional processing, is an important genetic risk factor for schizophrenia and brain development. Pergola et al. have shown that alleles that predict higher co-expression of these genes (labeled PCImiR-137) are associated with the increased activation of the PFC and connectivity during emotional processing. Interestingly, this same index (PCImiR-137) was negatively associated with improvement in negative symptoms in patients with schizophrenia

after short-term treatment with antipsychotics. Thus, a higher expression of genes from the group associated with lower miR-137 expression leads to less improvement in negative

symptoms, while simultaneously increasing neural activity in the PFC during emotional tasks, suggesting a compensatory mechanism or neural inefficiency.<sup>17</sup>

## CONCLUSION

Emotional processing in patients with schizophrenia is greatly impaired, causing difficulties in social functioning. Impairments of brain regions responsible for social cognition are associated with a reduced ability to recognize other people's emotions. In addition, there is a change in the connectivity of the brain regions with dopaminergic centers, between the salient networks, temporal, and frontal lobes, which contributes to impaired speech perception and cognitive deficits, indirectly impacting emotional processing. Low brain pH in patients with schizophrenia might be a possi-

ble therapeutic target, since it is associated with a disruption of dopamine and glutamate transmission and changes in the function of NMDA receptors, which lead to both positive and negative symptoms. Altering the brain pH and function of affected receptors might improve these symptoms as well as emotional processing. The low miR-137 expression leads to less improvement of negative symptoms and is involved in emotional processing, making its target genes another possible therapeutic target and new treatment options for schizophrenia. All of these findings show how complex emotional processing is in individuals with schizophrenia, and are a basis for future research and treatment development to improve the patient's quality of life and social interactions.

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## OBRADA EMOCIJA U SHIZOFRENIJI

### Sažetak

Shizofrenija je teški psihijatrijski poremećaj karakteriziran pozitivnim, negativnim i kognitivnim simptomima. Jedna od glavnih značajki je deficit emocionalnog i socijalnog razumijevanja. Pacijenti često ne uspijevaju adekvatno detektirati i interpretirati emocionalne podražaje što doprinosi lošem funkcioniranju. Funkcionalne MRI studije otkrile su smanjenu aktivaciju u medijalnom prefrontalnom korteksu, amigdali i insuli, a oni su središta socijalne kognicije. Hiperaktivnost u amigdali i prefrontalnim područjima povezana je sa slušnim verbalnim halucinacijama kod kojih je prisutan emocionalni sadržaj. Poremećena neurotransmisija se molekularno objašnjava promjenom pH vrijednosti mozga koja prvenstveno utječe na funkciju NMDA receptora, noradrenergičku signalizaciju i sinaptičku plastičnost. Genetski faktor rizika za shizofreniju je promijenjena ekspresija miR-137 koja doprinosi abnormalnoj prefrontalnoj aktivaciji tijekom emocionalne obrade. Ovi nalazi dokazuju složenost emocionalnih simptoma kod pacijenata koji su dijagnosticirani sa shizofrenijom.

**KLJUČNE RIJEČI:** dopamin, miR-137, obrada emocija, shizofrenija, slušno-verbalne halucinacije