

Trends in Psychiatry and Psychotherapy

ISSN: 2237-6089

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Associação de Psiquiatria do Rio Grande do Sul

Brasil

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Frontal lobe alterations in schizophrenia: a review
Trends in Psychiatry and Psychotherapy, vol. 38, núm. 4, octubre-diciembre, 2016, pp. 198-206
Associação de Psiquiatria do Rio Grande do Sul
Porto Alegre, Brasil

Available in: http://www.redalyc.org/articulo.oa?id=311049080003



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### Frontal lobe alterations in schizophrenia: a review

Alterações no lobo frontal na esquizofrenia: uma revisão

Ateeg Mubarik,1 Hassaan Tohid2

#### **Abstract**

**Objective:** To highlight the changes in the frontal lobe of the human brain in people with schizophrenia.

**Methods:** This was a qualitative review of the literature.

**Results:** Many schizophrenic patients exhibit functional, structural, and metabolic abnormalities in the frontal lobe. Some patients have few or no alterations, while some have more functional and structural changes than others. Magnetic resonance imaging (MRI) shows structural and functional changes in volume, gray matter, white matter, and functional activity in the frontal lobe, but the mechanisms underlying these changes are not yet fully understood.

**Conclusion:** When schizophrenia is studied as an essential topic in the field of neuropsychiatry, neuroscientists find that the frontal lobe is the most commonly involved area of the human brain. A clear picture of how this lobe is affected in schizophrenia is still lacking. We therefore recommend that further research be conducted to improve understanding of the pathophysiology of this psychiatric dilemma.

**Keywords:** Schizophrenia, frontal lobe asymmetries, frontal-hallucinations, neuroimaging.

#### Resumo

**Objetivo:** Descrever as alterações no lobo frontal do cérebro humano em indivíduos com esquizofrenia.

Métodos: Esta foi uma revisão qualitativa da literatura.

Resultados: Muitos pacientes esquizofrênicos exibem anormalidades funcionais, estruturais e metabólicas no lobo frontal. Alguns pacientes apresentam poucas ou nenhuma alteração, ao passo que outros apresentam mais alterações funcionais e estruturais quando comparados com seus pares. A ressonância magnética é capaz de demonstrar alterações estruturais e funcionais em volume, substância cinzenta, substância branca e atividade funcional do lobo frontal, porém os mecanismos subjacentes a essas alterações ainda não são completamente compreendidos. Conclusão: Quando a esquizofrenia é estudada como um tópico central na área da neuropsiquiatria, os neurocientistas observam que o lobo frontal é a área do cérebro humano mais comumente envolvida. Uma imagem clara de como esse lobo é afetado na esquizofrenia permanece inexistente. Portanto, recomendamos que mais pesquisas sejam conduzidas para melhorar nosso entendimento sobre a fisiopatologia desse dilema psiquiátrico.

**Descritores:** Esquizofrenia, assimetrias do lobo frontal, alucinações – frontal, neuroimagem.

### Introduction

It has been well-established in recent times that schizophrenia can no longer be treated as an exclusively psychological or psychiatric phenomenon, since its pathophysiology involves a combination of neurological and psychiatric phenomena.<sup>1</sup> Therefore, it is more appropriate to study it as a neuropsychiatric disorder.<sup>2</sup>

The parts of the brain most commonly involved in schizophrenia are the forebrain, the hindbrain, and the limbic system.<sup>3-6</sup> According to some researchers, schizophrenia may be caused by alterations in the functional circuits in the brain, rather than a single abnormality in one part of the brain.<sup>7</sup> Not much is known about the brain areas involved in schizophrenia yet. However, it is believed that the temporal lobe, limbic

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Submitted Dec 14 2015, accepted for publication May 20 2016. No conflicts of interest declared concerning the publication of this article.

Suggested citation: Mubarik A, Tohid H. Frontal lobe alterations in schizophrenia: a review. Trends Psychiatry Psychother. 2016;38(4):198-206. http://dx.doi. org/10.1590/2237-6089-2015-0088

system (specifically the cinqulate gyrus, the amygdala, and the hippocampus), frontal lobe, cerebellum, and thalamus could be involved.8-10 Structural magnetic resonance imaging (MRI) studies indicate changes in the neuroanatomy of the cerebral hemisphere. Most of these changes are found in the forebrain. However, the emergence of functional MRI (fMRI) has revolutionized the field of neuroscience,11 enabling us to understand brain function with far greater precision, improving understanding of concepts involved in complicated topics such as the mirror neuron system. 12 Some of the most interesting findings of structural MRI and fMRI studies with schizophrenic patients include decreased gray matter (frontal lobe) volume, and reduced brain activity and volume.13 The ventricles and the basal nuclei in the brains of schizophrenic patients are often found to be larger than normal, whereas the hippocampus and amygdala are found to be smaller.14

The association with the frontal lobe has been studied most often, although all of the lobes are commonly involved, including the occipital lobe. 15 It is well known that many schizophrenic patients have some frontal lobe alterations and in this review we will focus on some of the frontal lobe alterations seen in schizophrenia. Questions that remain unanswered include whether the whole frontal lobe is involved or just some parts of it, which lobe is affected first if some lobes are affected before the others, and if some lobes are indeed affected before others in schizophrenia, whether the frontal lobe is the first lobe to be affected. Furthermore, debate is still ongoing with relation to the extent of the structural, functional, and neurochemical changes that are seen in the frontal lobes of these patients and this is a topic about which better understanding and greater knowledge are needed if the illness is to be properly understood. This, in turn, would not only expand our knowledge about schizophrenia, but would also open doors for better treatment and management of schizophrenia in the future.

There are few articles describing research studying schizophrenia in terms of its pathophysiology that have discussed all three aspects of the changes to the human brain seen in schizophrenia. Therefore, in this article we will review the anatomical, physiological, and metabolic changes in the frontal lobe of the human brain in schizophrenia.

# Physiological changes in the frontal lobe in schizophrenia

Schizophrenia brings about a variety of functional changes in the frontal lobe of the brain. It is already well

known that hallucination is one of the major symptoms of schizophrenia. Evidence indicates that the gray matter volume of the bilateral frontal lobe is negatively correlated with hallucinations.16 A deficiency in the capacity of dopamine release in the dorsolateral prefrontal cortex has also been studied in schizophrenia.<sup>17</sup> In addition to hallucination and other common symptoms, suicidality is a serious complication of schizophrenia. These patients are at increased risk of suicide and the risk is directly related with prefrontal cortex-based circuit dysfunction.18 Suicidal behavior is also associated with lower controlrelated activity in the premotor cortex.18 Past suicidal ideation is linked with lower activation in response to goal-representation demands in multiple prefrontal cortex (PFC) regions. Patients with past suicidal ideation have been linked with lower control-related activation in the premotor cortex on the same side as the active primary motor cortex.19

Reductions in fractional anisotropy are seen in the left anterior medial orbitofrontal cortex, in anterior cingulate cortex (mOFC-rACC) connections, and in bilateral posterior mOFC-rACC connections. Moreover, decreased fractional anisotropy in left posterior mOFC-rACC coupling has been found to be linked with more intense anhedonia-asociality and avolition-apathy.<sup>20</sup> Furthermore, weaker deactivation of the medial prefrontal cortex was observed when subjects diagnosed with schizophrenia or schizoaffective disorder were shown angry and neutral faces.<sup>21</sup>

In terms of functional activity, reduced functional activity is observed in the precentral gyrus, post central gyrus and ipsilateral cerebellum.<sup>22</sup> Moreover, reduction in the activity of the dorsolateral prefrontal cortex has also been observed, and there is occasional compensatory activity augmentation in the other prefrontal cortex regions.<sup>23</sup> Kim et al. studied frontal lobe activity patterns in schizophrenia patients using human face distracters during working memory maintenance. They found decreased activity in the superior frontal gyrus, dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, anterior cingulate cortex, inferior parietal gyrus, and fusiform gyurs.<sup>24</sup>

The relationships between cognition and schizophrenia and other psychiatric disorders have been the focus of a huge amount of research in the recent literature. Disturbances in cognitive control related to prefrontal cortex dysfunction have been found in schizophrenia. Alterations in local circuit function supporting high frequency oscillatory activity in the prefrontal cortex are the main pathophysiological mechanism of impaired cognitive control in schizophrenia.<sup>25</sup> Lewis et al. have stated that people with schizophrenia exhibit a signaling deficit through the TrkBneurotrophin receptor

leads to reduced GABA synthesis in the paravalbumincontaining subpopulation of inhibitory GABA neurons in the dorsolateral prefrontal cortex. This deficiency in perisomatic inhibition of pyramidal neurons contributes to decreased capacity of the gamma frequency synchronized neuronal activities that are fundamental for working memory function.<sup>26</sup>

Another interesting finding is an alteration to the blood supply to the frontal lobes of schizophrenic patients. Significantly lower OxHb is found in schizophrenia patients, suggesting abnormal blood supply.<sup>27</sup> According to Radhu et al., long interval cortical inhibition in the dorsolateral prefrontal cortex was dramatically reduced in schizophrenia patients, in comparison with healthy individuals, and is also specific to schizophrenia and markedly greater than seen in patients suffering from obsessive compulsive disorder.<sup>28</sup> In apparent contradiction of those findings, another study concluded that the negative symptoms in schizophrenia are mostly due to left temporal lobe dysfunction, rather than frontal lobe involvement.<sup>29</sup> In another study, Lewis et al. strengthened the previous concept of cortical dysfunction. They stated that pyramidal cells in the prefrontal cortex of schizophrenia patients receive inhibitory input from the paravalbumin basket cells class of GABAergic neurons. These inhibitory signals are essential for proper cognitive functions. Disturbances to these inhibitory signals in the prefrontal cortex, causing impairment of cognitive function, is also prevalent in schizophrenic patients.<sup>30</sup> The glycosylation process is also disturbed in the frontal cortex of schizophrenia patients. This process is essential for adding glucosamine to substrates for proper intracellular trafficking and targeting and cellular function.31 Additionally, schizophrenia also presents with disturbances in hippocampus and prefrontal cortex functional connectivity (FC), which is associated with polymorphism of the ZNF804A gene.32 This causes differences in the oscillatory activity of hippocampal theta.32 Moreover, decreased resting state FC between the bilateral frontal pole and other cognitive-related areas, including the dorsolateral prefrontal cortex, medial prefrontal cortex, anterior cingulate gyrus, posterior cingulate cortex/precuneus, temporal cortex, and inferior parietal lobe has been observed in the brains of schizophrenia patients.33 Another study conducted by Duan et al. suggested that schizophrenic patients exhibit reduced FC with the frontal gyrus temporal gyrus, cerebellum posterior lobe (bilateral), precuneus, and cingulate cortex. Additionally, in the hippocampus there was a significant interaction effect of group and time for FC with frontal gyrus, cerebellum posterior lobe, posterior cingulate cortex and temporal gyrus. Furthermore, changes of hippocampal (bilateral) longitudinal

connectivity with the right middle frontal gyrus decreased with positive symptom scores in schizophrenics. The study also indicated that changes in longitudinal bilateral hippocampal connectivity with the right middle frontal gyrus can trigger positive symptoms.<sup>34</sup>

Drug abuse has been comprehensively studied in relation to schizophrenia. Methamphetamine abuse and dependence can cause schizophrenia-like psychotic features. According to Okada et al., decreased hemodynamic changes in the bilateral ventrolateral prefrontal cortex is a common pathophysiology behind methamphetamine-related psychosis and schizophrenia. Stysergic acid diethylamide can also cause schizophrenia by altering transcriptional regulation in the prefrontal cortex. However, drug-induced psychosis and schizophrenia is a lengthy subject and warrants a separate research article.

Verbal fluency tasks activate the frontal lobe, but considerably decreased frontal lobe activation was observed in schizophrenia patients during both English and Chinese verbal fluency tasks.<sup>37,38</sup> Another important feature of schizophrenia is thought disorder. Thought disorder is considered to be caused by abnormalities of the left ventrolateral prefrontal cortex.<sup>39</sup> Furthermore, there is greater hypofrontality in schizophrenia than in control or healthy groups<sup>40</sup> and changes in oxygenated hemoglobin in the frontal cortex have positive correlations with the severity of psychotic symptoms in schizophrenia patients.<sup>40-43</sup>

Walter et al. have discussed the absence of lateralization effect.<sup>44</sup> This absence suggests a lack of domain dominance effects in schizophrenia patients, compared to controls who exhibited left inferior frontal cortex domain dominance for the verbal working memory domain and right prefrontal cortex dominance for the spatial working memory domain.<sup>44</sup> Some other studies have demonstrated hemodynamic alterations in the frontal cortex of schizophrenia patients' brains.<sup>45,46</sup> Furthermore, working memory impairment in schizophrenia has consistently been associated with the prefrontal cortex.<sup>47</sup> Functional neuroimaging studies of schizophrenia have shown dorsolateral prefrontal cortex dysfunction during working memory tasks.<sup>48</sup>

It has also been proposed that early-course schizophrenic patients have more PFC glutamate, which might raise PFC FC. Experiments have shown that increased PFC connectivity in early-course schizophrenia patients can predict symptoms and diagnostic classification, but found little evidence for hypoconnectivity. However, hyperconnectivity was seen at the whole brain level.<sup>49</sup> Decreased prefrontal gray matter volume leads to impairment of executive functioning in many schizophrenic patients. Altered prefrontal area

is associated with duration of illness. The longer the duration of illness, the greater the reduction of gray matter volume in the left medial frontal gyrus.<sup>50</sup> Lower mean fractional anisotropy in the left frontal lobe has also been observed in schizophrenic patients.<sup>51</sup>

Kauppi et al. showed that increased polygenic risk for schizophrenia is linked with reduced stimulation variance in the right middle-superior prefrontal cortex (BA 10/11) and the right inferior frontal gyrus (BA 45). This was observed in both cases and controls and was not influenced by sex, age, or task performance, showing that dysregulation of frontal lobe physiology is hereditary. Moreover, a study on prefrontal currents observed that prefrontal currents at the peak of spindle stimulation are remarkably decreased in schizophrenics. 53

There is concrete evidence to indicate that the posterior cingulate and medial prefrontal cortices are involved in the neuropathophysiology of schizophrenia. Many patients exhibit remarkable negative effective connectivity from the left medial prefrontal to posterior cingulate cortex.<sup>54</sup> Furthermore, a study comparing deficit schizophrenic patients with non-deficit patients demonstrated weaker fronto-parietal and frontotemporal coupling in non-deficit schizophrenic patients.<sup>55</sup> In addition to the

changes to the frontal lobe mentioned above in relation to schizophrenia, patients with psychosis spectrum also exhibit alterations in the frontal region. Dorsolateral prefrontal cortex stimulation correlated with cognitive problems in psychosis spectrum patients. In the same study, psychosis spectrum patients had exaggerated responses to threatening facial expressions in amygdala, left fusiform cortex, and right middle frontal gyrus.<sup>56</sup>

Many functional connections within the mismatch detection network (inferior frontal gyrus with insula, putamen, and medial orbitofrontal cortex) were found to be affected in a study of schizophrenia sufferers conducted by Backasch et al. They also observed that stimulation of the disconnected orbitofrontal cortex was correlated with ego disruption in schizophrenics.<sup>57</sup> The diffusion tensor imaging technique has also been used to test water diffusivity in schizophrenia patients. Schizophrenic patients had increased axial and radial diffusivity measurements in the prefrontal cortex and temporal cortex.58 We can obviously expect more literature to be published in the near future regarding physiological changes to the frontal lobe in schizophrenia that will broaden our understanding regarding the functional alterations of the frontal lobe in these patients (Table 1).

**Table 1 -** Physiological changes in the frontal lobe in schizophrenia, including most of the functional changes in the frontal lobe of schizophrenic patients

- Increased axial and radial diffusivity measurements in the prefrontal cortex and temporal cortex.
- Reduced GABA synthesis and disruption of the glycosylation process are also common.
- Reduced hemodynamic changes in the bilateral ventrolateral prefrontal cortex in methamphetamine-related schizophrenia.
- Deficiency in dorsolateral prefrontal cortex activity and increased activity in other prefrontal cortex areas; and disturbance of cognitive control related with prefrontal cortex dysfunction.
- High frequency oscillatory activity in prefrontal cortex and decreased capacity for gamma frequency.
- Long interval cortical inhibition is considerably decreased.
- Altered prefrontal cortex functional connectivity and resting state functional connectivity between bilateral frontal pole and other cognitive-related areas like the dorsolateral prefrontal cortex and medial prefrontal cortex.
- Decreased frontal lobe activation during English, and Chinese verbal fluency task and decreased activity in the superior frontal gyrus, dorsolateral prefrontal cortex, and ventrolateral prefrontal cortex; dysfunction of dorsolateral prefrontal cortex, right middle-superior prefrontal cortex, and right inferior frontal gyrus; and prefrontal cortex based circuit dysfunction.
- Weaker fronto-parietal and frontotemporal coupling in non-deficit schizophrenic patients.
- Reduced functional connectivity (FC) with frontal gyrus temporal gyrus and right middle frontal gyrus.
- Suicidal ideation is linked with lower activation in response to goal-representation demands in multiple prefrontal cortex (PFC) regions.

## Morphological changes to the frontal lobe in schizophrenia

The frontal and temporal lobe tend to show reduced brain volume in patients suffering from schizophrenia. However, symptom severity and functioning level are not related with brain volume changes.<sup>59</sup> In contrast, less metacognitive insight is associated with decreased gray matter volumes in the left ventrolateral prefrontal

cortex, right dorsolateral prefrontal cortex and insula, bilateral premotor area, and putamen. This has also been associated with decreased white matter volumes of the right superior longitudinal fasciculum, left corona radiata, left forceps minor, and bilateral cingulum.<sup>60</sup> Pinner et al. investigated white matter connectivity changes in different brain regions and their relations with negative symptoms in chronic schizophrenia, reporting that myristoylated, alanine-rich C kinase substrate

(MARCKS) and (phosphorylated) pMARCKS expression were observed in the frontal cortex in schizophrenia, which is consistent with changed synaptic morphology and plasticity mediated by dysregulated cytoskeletal dynamics. 61 Motor areas in the brain and cerebellum have also been studied in relation to schizophrenia. Decreased gray matter was observed in the motor regions, while in the cerebellum, white matter volume was reduced.<sup>22</sup> Gray matter changes are not confined to motor areas. It has also been observed that gray matter cortex disappears in the anterior temporal lobe, insula, and medial frontal lobe and this loss developed a single spatial pattern even in a very diverse dataset.62 Furthermore, neuronal level alterations were also seen in the frontal lobe in schizophrenia patients.63 Anatomical changes at the cellular level in schizophrenia include reduced number of spines per dendrite and reduced length of dendrite.63 Moreover, there was destruction of pericapillary oligodendrocytes in the prefrontal cortex of schizophrenia patients. This could define new contours for a possible pathophysiology of blood-brain barrier abnormalities in schizophrenia patints.64

Psychotic diseases like schizophrenia and mood-related diseases like bipolar disease both lead to cognitive impairment. This impairment is thought to be due to reduced inferior frontal lobe volume. <sup>65</sup> The anatomical changes are also seen in people at high risk of schizophrenia. <sup>26</sup> For instance, significant cortical thinning, especially in the prefrontal cortex, anterior cingulate gyrus, inferior parietal cortex, parahippocampal cortex, and superior temporal gyrus, was observed in people with ultra-high risk of schizophrenia, as compared to controls. These changes in high-risk people correspond to the structural abnormalities found in schizophrenia. <sup>66</sup> Nodes of prefrontal-thalamic-cerebellar circuitry are also disturbed in patients with schizophrenia. <sup>67</sup> Sometimes treatment for schizophrenia can be detrimental to the frontal lobe

as well, since antipsychotic medications cause cortical thinning in prefrontal, temporal, occipital, and parietal lobes.<sup>68</sup> However, drug-induced frontal lobe alterations is a topic that needs to be better understood and more research papers are probably required.

Reduced cortical thickness and increased sulcal width in the frontal cortex has also been reported. Some patients have augmented sulcal width in all brain lobes. Moreover, research found that sulcal width was negatively correlated in the frontal cortex of a combined patient group.<sup>69</sup> In a study investigating urgency (rash or immediate action at impulse) in schizophrenic patients, Hoptman et al. demonstrated that urgency scores correlated with decreased cortical width in anterior prefrontal areas which include the medial and lateral orbitofrontal gyrus, the right frontal pole and inferior frontal gyri, and the rostral anterior cingulate cortex.70 First episode schizophrenia (FES) patients demonstrated remarkable regional white matter shortfall in the left inferior frontal gyrus. Moreover, FES patients and their non-schizophrenic siblings may both have white matter deficits in the left inferior frontal gyrus. These white matter deficits are supposedly associated with genetic factors related to schizophrenia susceptibility.71

Furthermore, delusional symptoms were negatively correlated with gray matter volume of both frontal and both temporal cortices, while hallucination symptoms negatively correlated with gray matter volume within the bilateral frontal, bilateral temporal, and left parietal cortices in schizophrenics.<sup>72</sup>

The structural abnormalities are obviously not confined to the frontal lobe; the left and right inferior temporal, right supramarginal/superior temporal, right and left inferiorfrontal, left frontopolar, right and left dorsolateral/ventrolateral prefrontal cortices, and the right thalamus are all affected, 73 including the hub nodes in frontal and temporal cortices (Table 2).74

**Table 2 -** Morphological changes to the frontal lobe in schizophrenia: possible anatomical changes including grey and white matter in the frontal lobe of schizophrenic patients

# Metabolic alterations in the frontal lobe in schizophrenia

Kynurenic acid levels were elevated in the prefrontal cortex in schizophrenia patients. High levels may play

a role in confusion and psychotic symptoms. This chemical acts as a glycine-site N-Methyl-D-aspartate NMDAr antagonist. It has been shown to play a role in glutamatergic neurotransmission. This is considered a part of the pathophysiology of schizophrenia.<sup>75-77</sup>

<sup>-</sup> Reduction in grey matter volume in the left ventrolateral prefrontal cortex and right dorsolateral prefrontal cortex; grey matter cortex loss in the anterior temporal lobe and insula; medial frontal lobe changes in the frontal lobe; and reduced inferior frontal lobe volume.

<sup>-</sup> Cortical thinning is also common, especially in the prefrontal cortex.

<sup>-</sup> Reduction in cortical thickness and increased sulcal width in the frontal cortex; white matter deficits in the left inferior frontal gyrus; disruption in nodes of prefrontal-thalamic-cerebellar circuitry; and grey matter cortex loss in the anterior temporal lobe, insula, and medial frontal lobe.

<sup>-</sup> Hallucination and delusion symptoms negatively correlated with grey matter volume of both frontal and both temporal cortices.

Kynurenic acid is produced by astrocytes from degradation of tryptophan. This endogenous Kynurenic acid regulates extracellular glutamate and acetylcholine levels in the prefrontal cortex. Kynurenine 3-monooxygenase and 3-hydroxyanthranilic deoxygenase activities are usually diminished in the prefrontal cortex of schizophrenic patients.78 Moreover, there is down-regulation of beta-1,4-mannosylglycoprotein 4-beta-N-acetylglucosaminyltransferase 3 and beta-galactoside alpha-2,3/6-sialyltransferase in the prefrontal cortex of schizophrenia patients.79 Decreased pH and increased lactic acid levels have also been found in schizophrenia patients' brains, but this was due to antipsychotic treatment rather than a primary abnormality in the prefrontal cortex.80 Reduced catabolism of N-acetylaspartate in oligodendrocytes due to deficiency of main enzymes has been observed and there were reduced acetate levels in the prefrontal cortex due to this abnormality. Acetate is mandatory for myelin lipid production and reduced levels may subsequently affect glutamatergic neurotransmission.81 Additionally, disturbance in purine metabolism probably exist that may play a role in prefrontal cortex impairment and cognitive disturbances in schizophrenia. 82 Hercher et al. also found glial abnormality in prefrontal white matter in schizophrenia patients. 83 Maternal inflammation disrupts metabolic function and myelin formation in the prefrontal cortex, which increases the risk of schizophrenia. 84,85

Schizophrenic patients had decreased Glutamate Glu (Glx) levels in the voxels of interest, while augmented levels were seen in patients with periodic and intense auditory hallucinations, relative to schizophrenics with less periodic and intense hallucination.<sup>86</sup> Moreover, remarkably lower GABA/Cr ratios were observed in patients with schizophrenia in the prefrontal cortex.<sup>87</sup>

As already discussed above, schizophrenics exhibit a deficit in the capacity for dopamine release in the dorsolateral PFC (DLPFC). Dopamine release in the DLPFC is related to working memory-related activation and this points toward a notion that blunted release may influence frontal cortical function.<sup>2</sup> Moreover, quantification by area to occipital ratio comparisons has shown that schizophrenic patients with positive symptoms have a hyper metabolic frontal metabolic pattern (Table 3).<sup>88</sup>

Table 3 - Metabolic changes in the frontal lobe in schizophrenia

- Dopamine level is affected in frontal cortices.
- Kynurenine 3-monooxygenase and 3-hydroxyanthranilic acid deoxygenase activities, beta-1, 4-mannosyl-glycoprotein 4-beta-N acetylglucosaminyltransferase 3 and beta-galactoside alpha-2, 3/6-sialyltransferase, glutamate Glu (Glx) levels, and GABA/Cr ratios are also reduced in the prefrontal cortex.
- Decreased pH and increased lactic acid levels are found in human brains in schizophrenia.
- Reduced acetate levels affect glutamatergic neurotransmission.

### Frontal lobe injuries

The frontal lobe is protected by the skull bone and so it is not easily damaged or affected by injury, but if a lesion does occur it can be extremely deleterious for the patient's wellbeing. Functions lost due to frontal lobe injuries include cognition, olfactory sensation,89 hand control, and speech. These functions are badly affected by even a slight lesion of the frontal region.89 Such lesions are not necessarily associated with a physical injury, but can also be caused by an infarction. Severe grasp reflex is observed in frontal lobe infarction and patients are unable to control the hand due to loss of white matter connection in frontal lobe white matter, while bilateral corticospinal tracts remain unaffected.90 Speech apraxia and aphasia is also related with the pattern of damage of cortical motor regions after stroke.91 Moreover, global aphasia without hemiparesis is observed in some patients, especially when there are anatomical lesions of the frontal lobe, sub-gyarl, sub-lobar, extra-nuclear, corpus callosum, and inferior frontal gyrus.92 Aphasia is also considered

a prognostic factor in frontal injuries.<sup>93</sup> Global aphasia without hemiparesis can progress to Wernicke's aphasia if the lesion is in the left precentral and postcentral gyri.<sup>94</sup> Patients with Broca's or Wernicke's area aphasia have hypoperfusion and hypometabolism of these areas.<sup>94</sup> Speech difficulties are frequently seen in schizophrenic patients. Therefore studies like those mentioned above<sup>92-95</sup> support the association of these areas (subgyarl, sub-lobar, extra-nuclear, corpus callosum, and inferior frontal gyrus) with schizophrenia. However, not much has been written about this association and a reasonable explanation is expected in the next few years.

## Other changes to the frontal lobe in schizophrenia

Encephalograms show augmented delta and theta activity in right frontal and right temporoparietal regions. <sup>96</sup> Moreover, a study on self-disorder which is a hallmark characteristic of schizophrenia showed that

schizophrenic patients demonstrate augmented local FC density in the frontal part of the brain.<sup>97</sup> A study using the Examination of Anomalous Self-Experience (EASE) scale showed that higher EASE scores (i.e., increased self disorder) are associated with lower peak parietal gamma frequencies and higher peak beta amplitudes over frontal and parietal electrodes in the left hemisphere following right-hand proprioceptive stimulation.<sup>98</sup> Studies like these have helped to fill gaps in knowledge of the pathophysiology of self-disorder.

#### Conclusion

Only studies investigating the human frontal lobe and schizophrenia have been included in this review. Since data from animal studies has been excluded, it is possible that some details related to frontal lobe changes in schizophrenic patient could have been omitted.

In conclusion, Schizophrenia is a neuropsychiatric disorder in which structural, functional, and metabolic changes to the frontal lobe are involved. There is more data on the physiology of frontal lobe involvement in schizophrenia than on the anatomy or chemistry of the brain. Some interesting findings from research articles have been compiled in this review to enable readers to acquire a better understanding about the nature of frontal lobe involvement in the pathophysiology of schizophrenia. Data on the functional aspect of frontal lobe involvement is undoubtedly very extensive, but a clear picture of the complete pathophysiology is still lacking. We therefore recommend that more research should be conducted in the near future to further investigate the functional, morphological, and metabolic alterations in schizophrenia, particularly in relation to the frontal lobe.

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