An Egg & Chicken Paradox: Are changes in the Basal ganglia volume the reason for or the result of Schizophrenia?

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Abstract

Magnetic resonance imaging (MRI) studies have demonstrated differences in the subcortical structure of schizophrenia patients compared to controls; nonetheless, it is not clear whether these changes are reason for or the result of schizophrenia (SZ). We aimed to investigate whether the basal ganglia volume was different in medication- naïve first episode schizophrenia patients. Seventy-one drug-naïve patients with first-episode psychosis (FEP) who applied to outpatient clinics and were diagnosed according to DSM-5 as well as 47 healthy controls (HC) were included in the study (n=118, 64 males, 54 females). T1-weighted images were acquired on a 1.5 T scanner (Magnetom SP, Siemens), and the basal ganglia volume was measured using the VolBrain software. Symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS) by an experienced psychiatrist. The volumes of right (R) and left (L) striatum, R- and L-caudate (CAU), and R- and L- Substantia nigra (SN) were found to be higher in FEP patients compared to the HC. The volume of L-putamen was higher, while that of the L- Globus pallidus (GP) and L-nucleus accumbens (NAcc) was smaller in FEP patients compared to HC. No significant correlation was found between volume measurements and PANSS scores. R-CAU, L-CAU, R-Striatum, L-Striatum, L-Putamen, L-NAcc, R-GP and L-SN were found to significantly predict psychosis in a Univariate Logistic Regression Model. Basal ganglia are affected from the first stage of the disease in schizophrenia, and it can be more possible that these changes are the result of pathogenesis schizophrenia.

Introduction

Schizophrenia (SZ) is a progressive chronic mental disorder that affects approximately 1% of the population and is usually first identified during late adolescence or young adulthood (Owen, Sawa, and Mortensen 2016). Positive symptoms such as hallucinations and delusions and negative symptoms such as amotivation, social withdrawal, apathy as well as cognitive impairment are among the important characteristics of SZ.

Basal ganglia are a group of subcortical brain structures located in the telencephalon, diencephalon and mesencephalon. These structures play essential roles not only in motor functions, but also cognitive and affective functions via two main pathways that are called direct and indirect (Gunaydin and Kreitzer 2016). The basal ganglia have connections with the cortex and thalamus via these pathways using the main neurotransmitters (NT) of these pathways: dopamine and glutamate (Figure 1). Motor and movement disorders of the basal ganglia have been a focus of research particularly for Parkinson's disease and Huntington's disease. Nonetheless, a role of the basal ganglia in psychiatric disorders, especially with the discovery of its role in cognitive and affective functions, has been examined as well (Calabresi et al. 2014).

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Considering the important role played by the NTs dopamine and glutamate and the presence of high levels of D2 receptors, it is not surprising to observe structural and functional anomalies of the basal ganglia in SZ. It is also thought to play a role in the pathogenesis of SZ due to its involvement in emotional and cognitive functions through the cortico-thalamic-striatal-cortical circuit. A significant impairment of these functions has been associated with SZ (Peters, Dunlop, and Downar 2016). Previous studies have supported a role of the basal ganglia in understanding the pathophysiology of SZ. However, the data obtained from both functional and structural MRI studies are not consistent. While some studies reported that across task domains, patients with SZ showed markedly decreased activation in the basal ganglia relative to healthy controls, others showed increased functional integration in the caudate nucleus (Albacete et al. 2019). In a meta-analysis with 2028 schizophrenic patients and 2540 controls, larger volumes of the pallidum and lateral ventricular were detected, along with a reduction in the size of the hippocampus, amygdala, thalamus, and accumbens in SZ patients compared to controls (Van Erp et al. 2016). Moreover, while some studies showed increased volumes of the caudate, putamen, and thalamus in first-episode psychosis (FEP) patients compared to healthy controls (HC), others indicated decreased volumes or no change (Crespo-Facorro et al. 2009; Lang et al. 2001; Makowski et al. 2016). Finally, there is a lack of consensus in the outcomes of neuroimaging studies due to the use of different volumetric measurement methods, different patient populations and especially since the effects of medications were not excluded.

In the present study, we hypothesized that the volume of basal ganglia was greater at the first instance of psychosis and we aimed to investigate whether the basal ganglia volume was different in medication-naive first episode SZ patients.

Methods

2.1. Participants:

The current study included seventy-six drug-naïve patients with FEP who applied to the psychiatry outpatient clinic of Bakirkoy Prof Mazhar Osman Training and Research Hospital. Two senior psychiatrists independently diagnosed the patients as having schizophrenia on the basis of the Structured Clinical Interview for DSM-5 Disorders- Clinician Version (SCID-5-CV). These patients were observed by these psychiatrists over a period of two months. At the end of this period of observation, 5 patients were removed from the study because of a change in their diagnosis from SZ. The control group (healthy control; HC) consisted of 47 individuals who were matched for age, gender, and body mass index (BMI) with the patients. HCs were selected from individuals who applied to the polyclinic for administrative procedures or from the hospital staff who were routinely examined within the scope of occupational health and safety laws. All participants were between the ages of 18-50 years. All of the participants were literate, and had no known mental disability that would prevent them from participating in the study. Additionally, none of the participants had a diagnosis of any chronic systemic diseases or neuropsychiatric diseases (relevant to the HC group only), or had a personal or family history of neurodegenerative disorders. Additionally, none of the participants used any drugs. Participants who were diagnosed with substance-alcohol use according to DSM-5 criteria were excluded from the study. Urine tests were performed on all participants to exclude any potential incidence of substance or alcohol abuse. The sample size was calculated by evaluating the effect size as 0.4, α-error as 0.05, power as 0.85 and G Power as 3.1.9.2. *2.2.*

Ethical approval

All participants were informed about the study procedures prior to the start of the study and written consent was obtained. Only those individuals who agreed to participate in the study were included in the final cohort. Ethical approval for the study was obtained from an Ethics Committee (reviewer blinded) (IRB Date/Number: 13. May 2022- 22/275).

2.3. Study procedure

FEP patients and HC who met the inclusion criteria of the study were directed to the research team by their physicians. After informing the FEP patients, the HC were also informed about the study, and written

informed consent was obtained from those who agreed to participate. Later, sociodemographic and clinical data forms were filled by all participants. Finally, brain MRI images of all participants were obtained. For patients, brain MRI was performed before starting treatment.

2.4. Clinical Scales

A sociodemographic data form was used to obtain data on age, gender, level of education, marital status, smoking and level of income from both the patient and control groups. In addition, the Positive and Negative Syndrome Scale (PANSS) was used to assess the severity of disease in FEP patients. The scale, which was developed by Kay et al., is a semi-structured interview scale that consists of 30 components and a severity evaluation of 7 points. It consists of 3 fundamental sub-groups; 7 out of 30 components are for positive symptoms, 7 for negative symptoms and 16 comprise a general psychopathology scale (Kay et al. 1987).

2.5. MRI Acquisition

MRI images of the patients were obtained with a 1.5T MRI device (Magnetom AERA, Siemens, Erlangen, Germany). High-resolution T1-weighted magnetization prepared rapid gradient echo (MPRAGE) images covering the whole brain were analyzed. Specified sequences were used with over one year of data acquisition (176 slices, FOV = 256 *256, 1 mm isotropic voxels, TR = 5.8 ms, TE = 3.3ms). MRI images were corrected for non-homogeneities in the magnetic field according to the method described by Sled et al. (Sled, Zijdenbos, and Evans 1998).

2.6. Volumetric Analysis

VolBrain, a fully automatic segmentation tool, which segments and quantifies the volumes of basal ganglion including the putamen, caudate, substantia nigra (SN), globus pallidus (GP) and NAcc was used in the current study (https://www.volbrain.upv.es). volBrain is a pipeline to automatically analyze MRI data through the web. Different types of scans including T1 and T2 weighted scans can be utilized in volBrain. It also uses multi-atlas label fusions to provide volume information(Hasan, 2021).

VolBrain was reported to show superior accuracy in segmenting all seven subcortical structures [26] compared to other publicly available software packages such as FreeSurfer (Fischl et al. 2002) and FSL-FIRST (Patenaude et al. 2011). All MRI images were checked and corrected manually, if necessary.

2.7. Statistical Analysis

Data were analyzed with the Statistical Package for Social Sciences for Windows (SPSS) version 25.0. The study data were evaluated with various descriptive statistical methods such as frequency, percentage, mean and standard deviation. The Kolmogorov Smirnov test was used to determine whether the variables conformed to a normal distribution. Categorical variables were compared using the Chi-square and Fisher's test. The Mann-Whitney U and Student t tests were used to compare the volumetric data between independent control and patient groups. Pearson correlation test was used to examine correlations between basal ganglia volume data and PANSS scores. A logistic regression model was used to determine whether basal ganglia volume could predict the diagnosis of FEP patients. All statistical tests were two-tailed, and significance was determined at the level of $p<0.05$.

Results

3.1. Demographic and clinical data

The study population consisted of 64 males (54.2%) and 54 females (45.8%). The average age of the HC and FEP patients was 31.60 ± 8.2 and 30.90 ± 8.5 years, respectively. There was no significant difference in age ($p = 0.21$), gender ratio ($p = 0.57$), education level ($p = 0.33$) or marital status ($p=0.53$) between the study groups. The incidence of smoking was significantly higher in the FEP group ($p=0.02$). The average age of disease onset for FEP was 29.2 ± 8.2 years. Detailed clinical data and demographic information are shown in **Table I.**

3.2. Evaluation of basal ganglia volumes and correlation with PANSS scores

A comparison of the basal ganglia volumes (cm³) between the patients with FEP and the HC is shown in **Figure 2** . The volumes of right (R) and left (L) striatum, R- and L-caudate, and R- and L- SN were found to be higher in FEP patients compared to HC (P<0.0001, P<0.0001, P<0.0001, P<0.0001, P=0.02, P<0.0001, respectively). While the volume of L-putamen was higher (P<0.0001), the volumes of L- GP (P=0.03) and L-NAcc (P=0.04) were found to be significantly smaller in FEP compared to HC. No significant correlation was found between volume measurements and PANSS scores. Statistical evaluation of the relationship between PANSS scores and basal ganglia volumes is shown in

Table II.

3.3 Evaluation of volumetric measurements to predict diagnosis in patients with FEP

Volumetric measurements that were used to predict the diagnosis of SZ are shown in **Table III** . A Univariate Logistic Regression Model suggested that the volumes of the R-caudate, L-caudate, R-striatum, L-striatum, L-putamen, L-NAcc, R-GP and L-SN could significantly predict the diagnosis of SZ. The volumes of the R-putamen, R-NAcc and L-GP did not have any predictive effect on the pathogenesis of SZ**.**

Discussion

In the current study, basal ganglia volumes were evaluated in medication-naïve patients with FEP and compared to that of the HC group. A remarkable finding of the current study is that almost all basal ganglia volumes were higher in patients with FEP compared to the HC group.

Basal ganglia contribute to many cognitive processes such as decision making, behavior planning as well as motor movements. These nuclei mediate such important functions by communicating with each other and with the cortex. While the basal ganglia play a role in the regulation of motor functions through the dorsal corticostriatal circuit, it also plays a role in cognitive and sensory functions through the ventral corticostriatal circuit (Calabresi et al. 2014). The caudate nucleus, one of the two parts of the striatum, is especially involved in the ventral circuit, while the other part, the putamen, is mostly involved in motor functions in the dorsal circuit **(Figure 1)** . Moreover, it plays a role in the reward circuit by communicating with the limbic system via the NAcc (Nicola 2007). This communication is carried out via two pathways: direct and indirect (Calabresi et al. 2014), with the use of activating neurotransmitters such as glutamate and inhibitory neurotransmitters such as GABA. In both pathways, the cortex stimulates the striatum via glutamate, while the striatum inhibits the GP via GABA. In addition, the dense D1 and D2 receptors in the striatum are the targets of dopamine that is released from the SN (Calabresi et al. 2014).

Studies conducted in recent years indicate that these circuits are impaired in many psychiatric diseases, especially in SZ. Both functional and structural anomalies have been shown to occur in the basal ganglia (Peters, Dunlop, and Downar 2016). Several studies have reported data for individual basal ganglia. PET studies of SZ patients showing imaging data of subdivisions of striatal function have shown that the greatest difference in dopamine function was within the associative striatum; additionally, differences in the limbic subdivision are also possible (R. A. McCutcheon, Abi-Dargham, and Howes 2019). A meta-analysis found that dopaminergic function was significantly increased in the sensorimotor regions, but not significantly in the limbic subdivision in patients compared to controls (R. McCutcheon et al. 2018).

Studies investigating presynaptic dopamine function in individuals at ultra-high risk of psychosis (UHR) have reported that the greatest abnormality was in the associative striatum. Exacerbation from UHR to psychosis was associated with a progressive increase in dopamine synthesizing capacity (O. D. Howes et al. 2009; Mizrahi et al. 2014). No significant changes were observed in the limbic subdivision at the dorsal striatum (O. Howes et al. 2011). On the other hand, fMRI studies have shown hypo-connections between the cortex and the dorsal striatum in patients with SZ (Fornito et al. 2013; Horga et al. 2016; Yoon et al. 2013, 2014), UHR individuals (Dandash et al. 2014), and individuals carrying a genetic risk for the development of psychosis (Fornito et al. 2013).

Greater activity in the dorsal striatum, measured by MRI at a resting state, was shown to correlate with psychotic symptoms (Sorg et al. 2013). Treatment response in such patients correlated with increased functional

connectivity between the associative striatum and the prefrontal cortex (Sarpal et al. 2015). Meanwhile, studies using diffusion tensor imaging have reported reduced anatomical connectivity between the dorsolateral prefrontal cortex and the associative striatum in SZ patients (Levitt et al. 2017). However, it is important to recognize that some fMRI studies show changes in the ventral striatal function in patients with psychotic disorders compared to controls (Radua et al. 2015). Volumetric studies in which the putamen and caudatus were measured separately from the striatum, larger striatal volume was reported in patients with SZ (Simpson, Kellendonk, and Kandel 2010). In the current study, we also found both striatum volumes to be higher in the FEP group. There may be several reasons for this. In accordance with the dopamine hypothesis of SZ, increased dopamine levels in the nigrostriatal pathway may lead to excessive stimulation of striatal D2 receptors leading to larger striatum volumes (R. A. McCutcheon, Abi-Dargham, and Howes 2019). The glutamate hypothesis of SZ may also be implicated; excessive stimulation of the striatum by glutamate due to dysfunction of GABA interneurons may lead to an increase in striatum volumes. A decrease in the striatum volume observed with antipsychotic treatment also supports the relevance of neurotransmitters (Kreitzer and Malenka 2008).

The nucleus caudatus is involved in the ventral cortical circuit and takes part in cognitive functions and the reward pathway. Postmortem studies of SZ patients have revealed abnormal mitochondrial structures in the caudate nucleus glia and neurons (Roberts 2017).

Although low caudate volume was mostly detected in medication-naive patients in structural MRI imaging studies, studies with larger cohorts have revealed the presence of a larger caudate nucleus in SZ patients compared to healthy controls (Glenthoj et al. 2007). A meta-analysis has shown a decrease in the volume of caudate nucleus in patients, with no volume changes observed in response to treatment (Haijma et al. 2013). In the present study, we found that both caudate nuclei were larger in FEP compared to the HC. This difference from other published studies may have resulted from the use of thinner sections in the current study. In addition, the use of the VolBrain program, which is known to be more sensitive in the segmentation of subcortical structures, may also have affected the study results. However, it is not surprising to expect an increase in the volume of the caudate nucleus, which is particularly exposed to excessive stimulation by the SN and cortex, in accordance with the well-established SZ hypothesis.

The putamen is involved in the dorsal corticostriatal circuit and mediates the execution of motor functions (Calabresi et al. 2014). Although an increase in dopamine levels and an increase in activity in the dorsal striatal region were observed in fMRI and PET studies in SZ patients, no significant change in the volume of the putamen was reported in structural MRI studies (Van Erp et al. 2016; Haijma et al. 2013). However, the volume of the putamen is known to increase proportionally with the duration of disease and age (Van Erp et al. 2016). In the current study, the left putamen was found to be significantly larger in FEP patients, while the right putamen was similar to HC, consistent with data in the literature. The direct pathway is known to be more active in the left hemisphere while the indirect pathway is more active in the right hemisphere (Kalva et al. 2012), which may account for the difference in size of the right and left putamen in the current study. However, to substantiate this, PET and structural MRI studies should be performed together. GP is controlled by GABA neurons from the striatum. Stimulation of the striatum is known to inhibit the pallidum; moreover, the pallidum is active if the striatum is not stimulated (Calabresi et al. 2014). Previous studies have reported larger volume of the pallidum in SZ patients compared to controls (Van Erp et al. 2016). On the contrary, in the current study we found the pallidum volume to be smaller in patients with FEP. The previous studies had been carried out on patients under treatment; such studies were validated by a meta-analysis of the ENIGMA consortium and showed that treatment increased the pallidum volume (Van Erp et al. 2016). In the current study, high striatal volume may have caused a decrease in pallidum volume by suppressing the pallidum with excessive GABA secretion (Calabresi et al. 2014).

The NAcc is the primary structure of the reward pathway and is stimulated by the ventral corticostriatal circuit and the limbic system (Nicola 2007). The NAcc was shown to be associated with negative findings in SZ. Studies have shown a significant decrease in accumbens activity (Radua et al. 2015), while structural imaging studies have shown a decrease in the volume of the NAcc in SZ (Mikell et al. 2009). In the present

study, we also found that the volume of the left NAcc was significantly lower in SZ patients compared to the healthy controls. These data are consistent with the findings reported in the literature and the SZ hypothesis.

A modest negative correlation was identified between PANSS-negative symptoms and the volumetric measurements; nonetheless, the relationship did not reach statistical significance. SN is one of the main sources of dopamine in the brain and forms the nigrostriatal pathway, especially by interacting with the striatum and D2 receptors (Calabresi et al. 2014). Hypofunction of this pathway has been associated with the pathogenesis of Parkinson's disease (Sako et al. 2014). In addition, this pathway is a target of antipsychotic drugs and has been implicated in the incidence of extrapyramidal system (EPS) side effects (Albacete et al. 2019). Although a significant loss of volume of the SN has been reported for Parkinson's, there are no clear findings for SZ patients in the literature. To our knowledge, the current study is the first to measure the volume of the SN in SZ. Yoon. et al. reported the presence of task-evoked SN hyperactivity (Yoon et al. 2014); corroborating these findings, we found that both SN volumes were significantly higher in FEP patients. This was consistent with functional studies and the pathogenesis of SZ.

Limitations

The current study has some limitations that need to be considered while evaluating the results. Although our sample size was larger than other reported studies, it may not be enough to explain the volumetric abnormality of the basal ganglia in FEP patients. In addition, while different volumetric analysis methods were used in previous studies, we used the VolBrain method. The use of different methods can account for the differences in the results obtained. No other independent volumetric analysis methods were carried out to validate our results.

Conclusions

The primary finding of this study is that the volumes of the striatum, the nucleus caudatus, putamen and SN were increased in patients with FEP, while a decrease was found in the volumes of the NAcc and GP. These findings support the neurotransmitter hypothesis of SZ and show that the volume changes of basal ganglia are a result of pathogenesis of SZ. However, studies in which both structural and functional imaging methods are used together are needed to determine whether volumetric changes can account for the functional changes observed.

Author Contributions

UHY conducted the analyses and wrote the manuscript. MS collected data from patients and controls. NY and KBP contributed to the measurement of basal ganglia volume and volumetric analysis with volBrain. NK was responsible for oversight and coordination. All authors provided feedback and final approval on the manuscript.

Conflict of Interest

### Funding And Disclosure

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Figure I: The working principle of basal ganglia
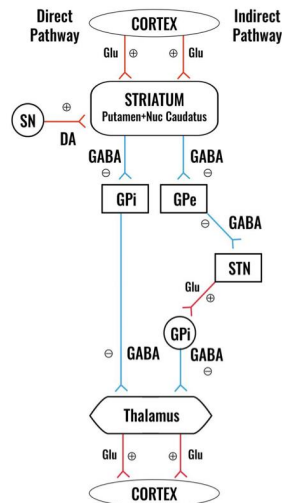
Glu: Glutamate, DA: Dopamine GPi: Globus Pallidus-interna, GPe: Globus Pallidus-externa SN: Substantia Nigra, STN: Subthalamic Nucleus

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Table 1 basalgang-2.docx available at https://authorea.com/users/572644/articles/617379-an-egg-chicken-paradox-are-changes-in-the-basal-ganglia-volume-the-reason-for-or-the-result-of-schizophrenia

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Figure II : Comparison of the basal ganglia volumes (cm³) between the patients with FEP and the HC. (mean ± sd)
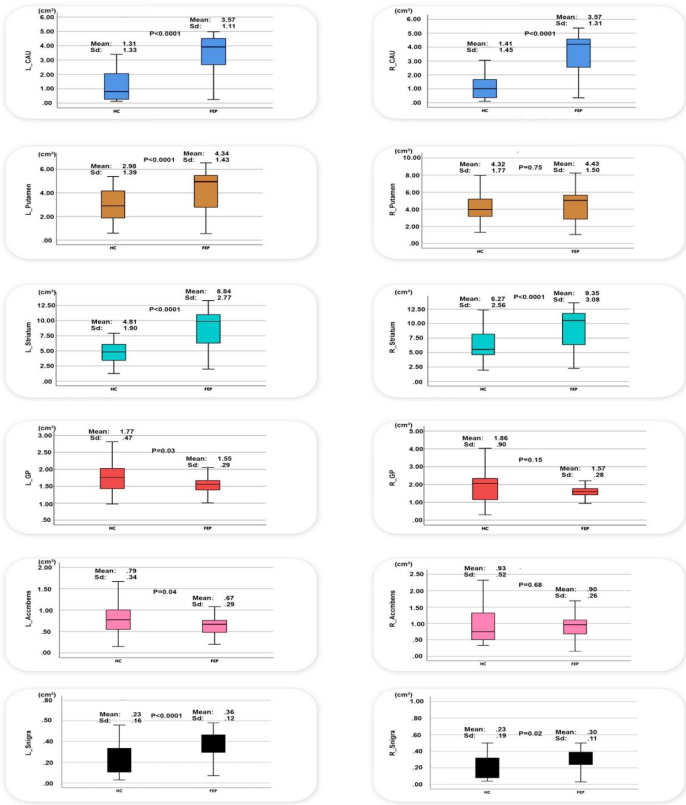
* p<0.05 **p<0.001, Chi-Square Test, Fischer Exact Test, Mann Whitney U test and Student t test were used for statistical analyses.R: Right, L: Left, FEP: First Episode Psychosis. ,CAU: caudate,, GP: Globus Pallidus

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`table-2 Correlation basal ganglia-2.docx` available at https://authorea.com/users/572644/articles/617379-an-egg-chicken-paradox-are-changes-in-the-basal-ganglia-volume-the-reason-for-or-the-result-of-schizophrenia

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