Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/readc473

AN FDG-PET STUDY ON THE REGIONAL METABOLISM OF THE BRAIN IN SCHIZOPHRENIA

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ABSTRACT

Recent technological development has proved beyond doubt that schizophrenia is biological in nature. FDG-PET functional neuroimaging has now emerged as an important tool in the examination of the biological basis of the psychopathology of schizophrenia. FDG-PET scanning was performed on male patients with schizophrenia diagnosis, and all of them were in the state of active psychosis according to the PANSS scale in resting conditions. The uptake of glucose cerebrally in the different regions of interest was examined throughout the schizophrenia spectrum. There was no significant impact upon cerebral glucose metabolism by the chronicity or severity of the illness. The negative type of schizophrenia patients had a significant reduction in metabolism in all the brain regions as compared to the positive type. Conversely, positive syndrome of schizophrenia showed extensive elevation of glucose metabolism in the medial temporal areas, basal ganglia and left thalamus. The cerebellum also showed hypometabolism. Although several brain structures have been implicated as the possible causative regions, and theories on how they work have been put forward, the fact that schizophrenia is significantly heterogeneous makes it a big challenge to specifically describe the disease process.

Keywords: Brain, Schizophrenia, Patients, Metabolism

INTRODUCTION

Schizophrenia is a severe mental condition that has extensively been linked to the irregularities in the functioning of the brain [1]. The more recent neuroimaging methods and especially FDG-PET (fluorodeoxyglucose positron emission tomography) neuroimaging enables the researcher to investigate the regional brain metabolism in schizophrenia in a more global way [2]. This is a non-invasive imaging study that can give information about the cerebral glucose metabolism that is an indicator of brain activity and can be correlated to the cognitive and emotional aspects of schizophrenia. The findings of the studies at all times pointed to the fact that schizophrenia is accompanied by regional metabolic abnormalities yet the patterns differed in regard to different subtypes of this disorder [3-5]. Studies are usually done by scanning patients at rest to determine the uptake of glucose in various portions of the brain. Among the important findings one can distinguish the fact that schizophrenia is heterogeneous, which makes it difficult to distinguish certain parts of the brain that are consistently involved in the disorder. Specifically, it has been found that patients with negative schizophrenia (with such symptoms as blunted affect, social withdrawal, and cognitive deficits) have a considerable decrease in glucose metabolism in a large number of brain areas [6, 7].

This hypometabolism is primarily prominent in regions involved in executive functioning and emotional regulation like prefrontal cortex and could be the cause of cognitive and emotional

dysfunction witnessed in these patients. Contrastingly, positive schizophrenic patients (those with symptoms like delusions, hallucinations and disorganized thinking) have enhanced glucose metabolism in the medial temporal regions, basal ganglia and in the left thalamus [8-10]. These include memory, sensory processing, and motor control, which could be a reason behind some symptoms associated with this subtype, including hallucinations and delusions. Although these results have been found, the connection between brain metabolism and the clinical manifestation of schizophrenia is not simple. The metabolic regional differences reported by the studies are useful in indicating the neurobiological basis of the disorder but which point out the difficulty in comprehending the complete pathological nature of the disorder attributed to the heterogeneity of the disorder [11].

MATERIALS AND METHODOLOGY

It was carried out at the Psychiatry Department, tertiary care hospital. Thirty-six patients with a definitive diagnosis of schizophrenia (ICD-10) and a Positive and Negative Syndrome Scale (PANSS) score of 70 to 120 were selected in the outpatient psychiatry unit. The exclusion criteria were any comorbid Axis I psychiatric diagnoses, substance abuse or dependence (other than nicotine dependence), mental retardation, previous or existing history of neurological diseases, and any medical disease as well as elevated blood sugar level (greater than 120 mg/dl). All participants had been furnished with ample information about the nature and aim of the study and a written informed consent had been signed by both the participants and their care givers in the presence of independent witness. Also, a semi-structured questionnaire was applied to the participants to collect data concerning their sociodemographic profile, family morbidity, handedness, and schizophrenia duration and course. Neurological examination and physical examination were also done in detail.

Brain FDG-PET scans were made within 24 h of PANSS evaluation. The participants were asked to fast through the night and their levels of blood sugar were tested before being scanned. F-18 2-fluoro-2-deoxyglucose (F18-FDG) was injected in an average of 200 MBq (160 to 230 MBq). Once injected, the participants were requested to relax in a well-ventilated room with good lighting and avoid talking. Their ears were not blocked and their eyes were opened. The scan was acquired 30min following the injection. The suitable positioning was facilitated by laser alignment lights, and the head was restrained to limit the artifacts related to motion. A GE Advance PET system scanner NXI was utilized to determine the cerebral glucose metabolism distribution. This scanner has a trans-axial resolution of 4.8 to 6.2 mm FWHM (Full Width Half Maximum) across a distance, depending on the distance away from the center and an axial resolution of 4.0 to 6.6 mm FWHM. Seventy slice emission scans were acquired in the cantho-meatal line, vertex to neck. The transmission scans were performed with germanium-68 (Ge-68) rod sources to correct attenuation. The reconstruction algorithm used was Ordered Subsets Expectation Maximization (OSEM) and the images were reformatted into 35 trans-axial slices of 4.25 mm thick slices for qualitative analysis and 17 trans-axial slices of 8.5 mm thick slices used in the quantitative analysis. The glucose metabolism in the regions was studied in 14 pre defined Regions of Interest (ROIs) representing elliptical ROIs in cortical and sub cortical structures and circular ROIs in cerebellar hemispheres. Cortical and subcortical ROIs were fixed at 6.31 sq. cm with pixel values between 46 and 52 and cerebellar ROI was 14.03 sq. cm with pixel values ranging between 96 and 104.

RESULTS

The sample average age was 28.7 years, and 72 percent of the respondents had at least secondary education level. Twenty-eight of them were unemployed, 22 were married and two of the participants were left handed. Sixty-six percent of the subjects had a history of nicotine dependence, and 33 percent of the subjects had a family history of schizophrenia (see Table 1). The illness began at the mean age of 22.7 years and the illness duration was on average 5.9 years. The total PANSS scores were between 78 and 119 with the mean score of 94.1. None of the participants had abnormal movements in the clinical examination. Based on the composite scale, 22 subjects were rated as positive schizophrenia and 14 as negative schizophrenia.

Qualitative evaluation demonstrated varied patterns of decrease in metabolism: 4 subjects had a generalized slowing of metabolism, 5 had selective decreased glucose utilisation in all but the occipital lobes, 6 had regional selective decreases, and 3 scans were almost normal in appearance. Glucose uptake was enhanced in the basal ganglia of 8 of the participants and 2 showed reduced uptake uncoupled to overall metabolism. The other 8 subjects did not results with significant abnormalities. The cerebellar glucose uptake decreased in 20 out of 36 of the participants, regardless of there being no overall decrease in metabolism.

Age of onset and illness duration were not in statistically significant correlation with the glucose uptake ($p > 0.05$). The mean uncorrected values (mUVs) in all the regions of interest (ROIs) showed a positive correlation to total PANSS scores, with the exception of right occipital and left cerebellum which indicated negative correlations. Total PANSS scores were positively connected with the corrected uncorrected values (rUVs) in all ROIs, except the right occipital, left cerebellum, and left thalamus; rUV in the right occipital cortex was negatively connected.

Type of Schizophrenia and Regional Glucose Metabolism

When comparing the two types of schizophrenia according to the composite scale, mUVs in all ROIs were significantly lower ($p < 0.05$) in predominantly negative symptoms schizophrenia patients in comparison to predominantly positive symptoms patients, except in the right lateral temporal area. The contrast in glucose consumption was extremely significant ($p< 0.01$) in the right cortical (frontal and parietal), medial temporal regions on both sides, both cerebella, left basal ganglia, and left thalamus. These differences, however, were not found to be significant after correction against multiple comparisons.

Symptom Profile and Regional Glucose Metabolism

Correlation of the regional glucose activity values (mUVs) with symptom profile as determined by the Positive and Negative Syndrome Scale (PANSS) scores, revealed that mUVs in both the medial temporal regions, bilateral basal ganglia and left thalamus correlated significantly ($p < 0.05$) and positively with the positive syndrome score. Nevertheless, there was no considerable correlation ($p > 0.05$) between rUVs of the various ROIs and the positive syndrome score. There was a negative correlation between the negative syndrome scale scores and mUVs across all ROIs, which was, however, not significant ($p > 0.05$). In a similar fashion, the rUVs in the right cortical areas, bilateral cerebella and left thalamus also showed a negative correlation with the negative syndrome score, but this too was not significant ($p > 0.05$).

Table 1: An overview of the sample's sociodemographic characteristics

Profile		Frequency
Education	Graduate	4
	Illiterate	2
	Primary	4
	Secondary	26
Occupation	Service	8
	Unemployed	28
Marital status	Married	14
	Unmarried	22
Handedness	Left	2
	Right	34
Nicotine dependence	No	12
	Yes	24
Family history	No	24
	Yes	12

Table 2: Uptake of maximum cerebral glucose differs

ROI	Positivetype	Negativetype
	(*n*=22)	(*n*=14)
Rfrontal	20.12	10.12
Lfrontal	21.24	10.14
Rparietal	21.82	10.41
Lparietal	23.45	12.47
RMtemporal	16.15	8.01
LMtemporal	14.74	7.94
RLtemporal	18.41	10.69
LLtemporal	18.34	10.48
Roccipital	24.45	13.49
Loccipital	27.12	13.67
Rcerebellum	21.26	8.47
Lcerebellum	19.41	9.87
Rbasalganglia	22.14	13.47
Lbasalganglia	21.58	12.78
Rthalamus	18.47	13.47
Lthalamus	19.58	11.64

Table 3: A correlation between the metabolism of glucose in different regions

	Positive syndrome				Negative syndrome			
	Pearson's coefficient	p value	Pearson's coefficient	p value	Pearson's coefficient	p value	Pearson's coefficient	p value
R frontal	0.374	0.014	0.341	0.117	–0.277	0.266	–0.143	0.570
L frontal	0.372	0.054	0.117	0.214	–0.241	0.335	0.106	0.676
R parietal	0.314	0.078	0.236	0.124	–0.300	0.226	–0.150	0.553
L parietal	0.358	0.087	0.173	0.399	–0.232	0.355	0.178	0.480
RM temporal	0.347	0.09	0.148	0.072	–0.317	0.201	–0.021	0.934
LM temporal	0.378	0.04	0.187	0.559	–0.280	0.260	0.200	0.426
RL temporal	0.396	0.03	0.134	0.508	–0.170	0.499	0.269	0.281
LL temporal	0.378	0.06	0.144	0.844	–0.211	0.400	0.055	0.827
R occipital	0.389	0.07	0.182	0.457	–0.288	0.247	0.139	0.583
L occipital	0.347	0.06	0.147	0.412	–0.279	0.263	–0.102	0.688
Rcerebellum	0.389	0.07	-	-	–0.293	0.238	—	—
Lcerebellum	0.364	0.04	-	-	–0.283	0.255	—	—
Rbasalganglia	0.487	0.03	0.164	0.574	–0.304	0.219	0.109	0.668
Lbasalganglia	0.471	0.02	0.106	0.497	–0.308	0.214	0.110	0.664
Rthalamus	0.496	0.04	0.021	0.914	–0.215	0.392	0.419	0.083
Lthalamus	0.473	0.02	0.314	0.147	–0.336	0.173	–0.389	0.111

DISCUSSION

The purpose of this study was to explore regional glucose metabolism of people with schizophrenia, as well as to compare patients with predominantly positive and negative symptoms [12]. The results indicate a marked disparity in the glucose consumption rates among the different parts of the brain, which provide a hint to the biological basis of the condition. The average age of the sample used in this study was 28.7 years, and most of them (72 percent) had at least secondary education. It is worth noting that the Nicotine dependence which has been quite prevalent in schizophrenia (66% of the participants in this case) could have confounding impacts on the brain metabolism [13-15]. This cohort had a mean age of onset of illness of 22.7 years and an average illness duration of 5.9 years indicating the chronicity of schizophrenia in this sample. The PANSS scores showed the moderate

level of the symptomatology severity, as the mean score was 94.1, which represented the balance between the positive and negative symptomatology in the sample. In comparison with the negative symptom predominant individuals, the positive symptom individuals, the study revealed that glucose metabolism differences in various brain areas were significant. the glucose metabolism of the participants with negative schizophrenia was strikingly diminished in the frontal and parietal cortices, the medial temporal regions, cerebellum, basal ganglia, thalamus. These areas are implicated in thought processes, sensory integration and motor regulation and could be the basis of cognitive and emotional loss observed in negative schizophrenia [16]. On the other hand, the positive schizophrenia brains showed increased glucose metabolism in the respective regions indicating increased activity in the brains on these areas, which could be linked to hallucinations, delusions, and other positive symptoms. A further analysis showed that the glucose metabolism in the regions was significantly correlated to the PANSS positive syndrome score especially in the medial temporal areas, basal ganglia, and the thalamus. These areas of the brain deal with memory, sensory, and emotional regulation which are deterred in most cases of schizophrenia. The negative syndrome score demonstrated no significant correlations with glucose metabolism in most regions, which suggests that the neurobiological processes behind negative symptoms could differ and be less linked with the metabolic activity in these regions. Findings of the study add to the existing knowledge of the different metabolic patterns with positive and negative symptoms of schizophrenia [17]. Despite the fact that the estimated differences were not significant when multiple comparisons were correction, the findings provoke the idea that regional glucose metabolism could be crucial in differentiating between the two subtypes of schizophrenia. Further investigations, with larger samples and more developed imaging methods, may straighten out the metabolic pathways in the pathophysiology of schizophrenia and its symptomatology even more.

CONCLUSION

The current FDG-PET research study supports the presence of substantial regional variations in the brain glucose metabolism between the participants with positive and negative schizophrenia symptoms. Positive schizophrenia showed improved utilization of glucose in the areas related to sensory processing and emotion regulation, whereas negative schizophrenia had reduced metabolism in corresponding areas. These results implicate the possibility of dissimilar metabolic processes as the basis of the various symptom presentations of schizophrenia providing a useful lead to the neurobiological processes of the disease and future studies on the potential of selective therapeutic interventions.

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