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Review article

Reprint of: $^{F\text{-}18}$Fluorodeoxyglucose positron emission tomography studies of the schizophrenia spectrum: The legacy of Monte S. Buchsbaum, M.D.

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ABSTRACT

This is a selective review of the work of Buchsbaum and colleagues. It revisits and pays tribute to four decades of publications employing positron emission tomography (PET) with $^{F\text{-}18}$fluorodeoxyglucose (FDG) to examine the neurobiology of schizophrenia-spectrum disorders (including schizotypal personality disorder (SPD) and schizophrenia). Beginning with a landmark FDG-PET study in 1982 reporting hypofrontality in unmedicated schizophrenia patients, Buchsbaum and colleagues published high-impact work on regional glucose metabolic rate (GMR) abnormalities in the spectrum. Several key discoveries were made, including the delineation of schizophrenia-spectrum abnormalities in frontal and temporal lobe, cingulate, thalamus, and striatal regions using three-dimensional mapping with coregistered MRI and PET. These findings indicated that SPD patients have less marked frontal lobe and striatal dysfunction compared with schizophrenia patients, possibly mitigating frank psychosis. Additionally, these investigations were among the first to conduct early seed-based functional connectivity analyses with FDG-PET, showing aberrant cortical-subcortical circuitry and, in particular, revealing a thalamocortical circuitry abnormality in schizophrenia. Finally, pioneering work employing the first double-blind randomized antipsychotic (haloperidol) vs. placebo FDG-PET study design in schizophrenia indicated that GMR in the striatum, more than in any other region, was related to clinical response.

1. Introduction

Over the past four decades, functional brain imaging techniques including positron emission tomography (PET) and, more recently, functional magnetic resonance imaging (fMRI) have allowed clinicians and neuroscientists to map brain regions and circuits associated with dysfunction in schizophrenia-spectrum disorders. These technologies allow for quantification of regional glucose metabolism and blood oxygenation level, which relate in surprisingly precise ways to the cellular activity of the brain (Raichle, 2009). This review paper focuses on the landmark early neuroimaging work of Monte Buchsbaum, M.D. and colleagues using PET to study the neurobiology of schizophrenia-spectrum disorders. This work was novel in its day and helped pave the way for current-day fMRI studies in the schizophrenia spectrum. Historically—PET with its spatial resolution in the 4 to 5 mm range—was used as a functional imaging tool to examine relative glucose metabolic rate (GMR) in the brain. After the advent of fMRI in the 1990s, which has the advantages of a short time resolution and no ionizing radiation, fewer studies used FDG-PET to study brain function in schizophrenia-spectrum disorders. Nevertheless, the early work of Buchsbaum et al. produced important findings on GMR in individual gyri of the cortex and discrete portions of the thalamus and basal ganglia, key regions for understanding the neural systems involved in thought disorder and medication response in schizophrenia.

This review focuses on select work from the extensive GMR literature in schizophrenia-spectrum disorders published by Buchsbaum and colleagues. A PubMed search on October 24, 2018 using the search term “Buchsbaum MS” listed 332 papers; adding “PET” to the search listed 88 papers. This review covers a subset of that work on schizophrenia-spectrum disorders.

2. Early days

In 1974, Ingvar and Franzen published the first paper examining

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regional cerebral blood flow (rCBF) in schizophrenia. They found that, compared with healthy controls (HCs), medicated chronic schizophrenia patients (n = 20) showed lower resting-state rCBF in frontal, compared with occipital lobes, yet the patients had normal overall CBF and oxygen uptake (Ingvar and Franzen, 1974). Ingvar hypothesized that this "hypofrontal" rCBF pattern may be a characteristic finding in chronic schizophrenia.

In the years that followed, a brain imaging approach was developed to directly measure regional cerebral glucose consumption in the brain using 2-deoxyglucose labeled with ^{18}Fluorine (fluorodeoxyglucose; FDG) together with PET. This method of examining cerebral glucose metabolism is thought to be a surrogate measure of neuronal activity. The key model for the utilization of glucose by the brain using FDG was developed by Sokoloff et al. (1977). The first application of FDG-PET in humans was conducted by Reivich et al. (1979) and validated by Phelps et al. (1979). The FDG radiotracer is injected into the participant via intravenous line while they are resting or engaged in a cognitive task in a sound-proof room. After approximately 32 min, the tracer is taken up by the brain and the participant is then moved to the PET scanner where the functional images reflecting brain work during the uptake condition are collected. The positrons emitted from the radiotracer interact with electrons in the participant's tissue to produce gamma rays that are detected by crystals in the PET scanner. These coincidence events are then calculated by the computer to form images illustrating the FDG uptake of the brain.

Although some preliminary findings in schizophrenia were reported (e.g., Ericson et al., 1981; Farkas et al., 1984), in 1982, Buchsbaum and colleagues at the National Institute of Mental Health (NIMH) showed for the first time that regional glucose metabolism in unmedicated schizophrenia patients differed from HCs using FDG-PET (Buchsbaum et al., 1982). Participants rested with their eyes closed during FDG uptake, replicating the conditions of Ingvar and Franzen's (1974) rCBF study. Buchsbaum et al. (1982) confirmed the finding of relative hypofrontality in schizophrenia using a sophisticated statistical approach. This multivariate mixed-model analysis of variance (MANOVA) involved repeated measures factors allowing for the examination of several dorsal-to-ventral axial PET slices of the brain subdivided into anterior-to-posterior quadrants (i.e. from front-to-back) and left and right hemisphere. Buchsbaum et al. showed that the front-to-back gradient in GMR was significantly lower in patients than HCs (Buchsbaum et al., 1982). This seminal work led to a significant increase in psychiatric research employing neuroimaging approaches to study schizophrenia. Dozens of FDG-PET studies (e.g., see reviews by Buchsbaum and Hazlett, 1998; Williamson, 1987) but not all, (e.g., Gur et al., 1995) subsequently reported hypofrontality in schizophrenia.

As reviewed below, early FDG-PET studies of the schizophrenia spectrum conducted by Buchsbaum and colleagues had a tremendous impact on the field and helped elucidate many of the factors related to the diagnosis and treatment of these debilitating disorders: regional brain abnormalities, functional connectivity abnormalities, medication effects on brain function, and diagnostic specificity. The early FDG-PET studies of Buchsbaum and colleagues were among the first to conduct neuroimaging investigations of regional functional abnormalities in schizophrenia, as they identified abnormal activity in the frontal lobe, striatum, thalamus, temporal lobe, and cingulate cortex prior to the advent of fMRI. While more recent work has focused on the relationships among brain regions (e.g., functional connectivity), we first review the early findings on the individual components of such circuits.

3. Frontal lobe

Following up on the earlier cerebral blood flow studies and the landmark FDG-PET study at NIMH in 1982, Buchsbaum et al. (1984) replicated the finding of a reduced anteroposterior gradient in schizophrenia. In this second FDG-PET study, rather than using an uncontrolled resting state during FDG uptake, patients were shocked on the forearm as a means of controlling the participants' mental activity. The abnormally low anteroposterior metabolic gradient pattern in schizophrenia did not appear to be correlated with clinical symptoms or severity of illness, and DeLisi et al. (1985a) hypothesized that it may represent a trait vulnerability. Once Dr. Buchsbaum moved to the University of California, Irvine in 1982, he began using a version of the degraded-stimulus Continuous Performance Test (CPT; (Nuechterlein et al., 1983) during the FDG-uptake period. The use of a CPT as the uptake task for FDG-PET was ideal as it had been shown to elicit poor performance in patients with schizophrenia and their offspring (e.g., Cornblatt et al., 1989; Cornblatt et al., 1988; Nuechterlein et al., 1983). In contrast to HCs, unmedicated and never-medicated schizophrenia patients demonstrated hypofrontality during this task (Buchsbaum et al., 1992a, 1990; Guich et al., 1989; Siegel et al., 1993). Next, Dr. Buchsbaum moved to The Mount Sinai School of Medicine in New York in 1992, where his team began using a task based on the California Verbal Learning Test (DeLisi et al., 1987) during the FDG-PET uptake period. Work using this serial verbal learning task (SVLT) confirmed hypofrontality in schizophrenia (e.g., Hazlett et al., 2000). This work also showed that, among the patients, more severe hypofrontality was associated with increased perseveration errors on the SVLT.

Collaborative work with Dr. Buchsbaum expanded upon explorations of frontal lobe abnormalities in the schizophrenia spectrum, including studies measuring psychophysiological responses during the FDG-uptake period. In 1989, Buchsbaum and colleagues (Guich et al., 1989) used 32-channel topographic EEG together with FDG-PET to show greater levels of delta activity in the frontal lobes of unmedicated schizophrenia patients compared with HCs. Additionally, greater frontal delta activity was correlated with less frontal lobe GMR (i.e. hypofrontality) in the patients. This work had important implications for understanding the neural substrates of EEG activity and abnormalities in delta activity in schizophrenia.

An early pilot study was the first to explore the neural substrates of one of the most consistent psychophysiological anomalies reported in schizophrenia (e.g., review by Holzman, 1987), namely a high incidence of skin conductance "nonresponders." Studies had shown that between 40–50% of schizophrenia patients failed to exhibit any skin conductance orienting response to mild stimuli, compared with only 5–10% of HCs. Using FDG-PET, Hazlett et al. (1993) reported that, "nonresponder" schizophrenia patients showed lower GMR than "responders" in lateral and medial frontal regions. Although preliminary, this finding was translational and suggested that frontal lobe regions may play an excitatory role in electrodermal activity in schizophrenia.

In a sustained selective-attention task involving attended, ignored, and novel tones that served as prepulses to a brief and startling pulse, Hazlett et al. showed that HCs exhibited greater prepulse inhibition (PPI) to the startle stimulus during attended than ignored prepulses, while the amount of PPI during novel tones was intermediate (Hazlett et al., 1998). In contrast, schizophrenia patients failed to show this normal pattern of differential PPI. HCs who exhibited the greatest PPI during the attended prepulse used their prefrontal cortex and suppressed their occipital lobe function. In contrast, unmedicated or drug-naïve schizophrenia patients who showed greater PPI used their prefrontal cortex to a much lesser extent and failed to suppress their occipital lobe function. This work replicated and extended hypofrontality findings to a novel attention-to-prepulse sensorimotor gating task in schizophrenia and was the first to combine a psychophysiological measure of sensorimotor gating (i.e. PPI) with functional neuroimaging.

In a follow-up study, Hazlett and Buchsbaum (2001) examined individual differences in attentional modulation of PPI and showed that, while the range for PPI during the attended prepulse was similar in both the HC and schizophrenia groups, the pattern of correlations between PPI during the attended prepulse and hypofrontality ratios was different

(Hazlett and Buchsbaum, 2001). Specifically, in HCs, better sensorimotor gating during the attended prepulse was associated with increased frontal lobe and decreased occipital lobe glucose metabolism (i.e. higher frontal/occipital ratio). In contrast, in the patient group, PPI during the attended prepulse was not correlated with hypofrontality ratios, suggesting dysfunction in the key top-down regions modulating the startle reflex.

In an exploration of the schizophrenia spectrum, Buchsbaum et al. (2002) found that prefrontal cortex and temporal lobe activity differed between unmedicated schizophrenia patients and individuals with schizotypal personality disorder (SPD), providing diagnostic specificity. Compared with HCs, lower GMR was found in dorsolateral prefrontal cortex (Brodmann areas 44, 45, 46) in schizophrenia patients, while SPD patients did not differ from HCs in these regions. Further, SPD patients showed higher-than-normal GMR in both medial frontal and medial temporal areas. In lateral temporal lobe regions, SPD patients had GMR values intermediate between those of HCs and schizophrenia patients. Of great interest, GMR in Brodmann area 10 of the prefrontal cortex was higher in SPD patients compared with HCs, suggesting a compensatory factor possibly protecting the SPD patient from frank psychosis. Abnormalities in the prefrontal cortex have been associated with disinhibition of striatal dopaminergic neurons, potentially leading to aberrant dopaminergic functioning (Meyer-Lindenberg et al., 2002). Siever and Davis (2004) postulated that prefrontal cortex reserves buffer against this cascade leading to striatal hyperdopaminergia, helping to explain the absence of frank psychosis in SPD.

4. Striatum

While the primary finding of the initial FDG-PET study from Buchsbaum et al. (1982) was lower GMR in the superior frontal cortex in schizophrenia patients compared with HCs, an important secondary finding was that the patients also showed lower GMR in the basal ganglia, primarily in the caudate nucleus. This work helped usher in early ligand studies examining dopamine receptors using PET (e.g., Wagner et al., 1983) and ^{18}F-DOPA work examining dopaminergic pathways (e.g., Garnett et al., 1982) in humans. In 1992, Buchsbaum and colleagues (Buchsbaum et al., 1992a) provided the first evidence of lower basal ganglia GMR in never-medicated schizophrenia patients compared with HCs (n = 18 vs. n = 20 HC) using a degraded-stimulus CPT during uptake. Thus, diminished ratios of inferior and medial frontal regions to occipital cortex, together with lower striatal GMR, suggested a combined frontostriatal dysfunction in schizophrenia.

One year later, an extended study with a much larger sample size (n = 70 schizophrenia vs. n = 30 HC) revealed basal ganglia GMR reductions in an unmedicated sample of schizophrenia patients during the same task (Siegel et al., 1993). At this juncture, it is important to note that Buchsbaum et al. and other research groups (e.g., Gur et al., 1995) had been employing an approach that identified key regions of interest using an MRI template to locate these small, variably-shaped caudate and putamen regions. However, in 1998, Buchsbaum and colleagues (Shihabuddin et al., 1998) combined structural MRI and FDG-PET in a novel approach to provide more accurate anatomical identification of the caudate and putamen for metabolic and size assessment in never-medicated or drug-free schizophrenia patients. This study showed that never-medicated patients had lower GMR in the right putamen compared with previously-medicated patients, and the caudate was smaller in never-medicated patients than HCs and largest in previously-medicated patients. This work was novel in its use of three-dimensional metabolic mapping of the striatum using MRI coregistration which allowed for tracing of the striatum entirely independent of the PET scan and laid the groundwork for future studies to employ seed analyses to examine functional connectivity. The findings of Shihabuddin et al. (1998) suggested the importance of antipsychotic medication exposure on both structural and functional neuroimaging. Shihabuddin et al. (2001) subsequently found that striatal activity differed between schizophrenia and SPD patients. Specifically, increased GMR in ventral putamen was evident in SPD compared with HCs, but it was reduced in schizophrenia. In SPD, higher ventral putamen GMR was associated with fewer psychotic-like symptoms, and thus it was hypothesized to be a protective factor against frank psychosis.

This early FDG-PET work stimulated the investigation of D1 dopamine receptors which are the main mediators of dopamine transmission in the cortex and subserve cognitive functions (e.g., working memory) that are adversely affected in schizophrenia patients. Examples include work showing an increase in frontocortical D1 receptor availability in antipsychotic-naïve schizophrenia patients which has been proposed to reflect compensatory, albeit insufficient, upregulation of D1 receptors in response to possible cortical hypodopaminergia in the schizophrenia spectrum (Abi-Dargham, 2003). More recent promising preliminary work examined whether a selective D1 receptor agonist (dihydrexidine, DAR-0100A) could attenuate working memory impairments in SPD. The findings indicate that pharmacological enhancement of D1 receptor activity may mitigate working memory weaknesses observed in the schizophrenia spectrum (Rosell et al., 2015).

5. Thalamus

The thalamus, a major cortical relay from the limbic system with many important frontal lobe connections, is of major interest in schizophrenia. Results from early FDG-PET studies of the thalamus in schizophrenia, (e.g., Buchsbaum et al., 1987; Resnick et al., 1988; Wiesel et al., 1987) were mixed, which was thought to be due to medication status, varied FDG-uptake conditions, or methodological issues with defining the thalamus visually vs. stereotaxically. In 1996, Buchsbaum et al. published the first evidence of reduced thalamic GMR in a never-medicated schizophrenia sample during the sustained-attention CPT (Buchsbaum et al., 1996). A few years later, Hazlett et al. (1999) employed novel methodology developed in the Buchsbaum laboratory to examine the thalamus. It involved using a sobel-gradient filter to enhance the gray/white matter edges on structural MRI, which allowed thalamic nuclei to be reliably traced (see Byne et al., 2001 for intertracer reliability details) on serial 1.2 mm thick MRI images for each participant. The structural MRI images were then coregistered to each participant's PET scan, and GMR in the thalamus and its nuclei was quantified. This methodology provided a more precise MRI-derived three-dimensional anatomic template of the thalamic nuclei hypothesized as dysfunctional in schizophrenia. This approach allowed a novel examination of the mediodorsal nucleus (MDN), the most prominent subcortical afferent to the prefrontal cortex. Impaired frontothalamic circuitry has long been implicated in schizophrenia; this study was able to assess that directly and, once again, was also novel in its inclusion of individuals with SPD. A key finding revealed lower GMR in the MDN bilaterally in the schizophrenia group, as compared to HC and SPD groups, whom did not differ from each other. Correlations indicated that, across the schizophrenia spectrum, individuals with greater clinical symptom severity (total Brief Psychiatric Rating Scale score; BPRS; Overall and Gorham, 1962) on the day of the PET scan had lower GMR in the MDN.

In the next study in this series, Hazlett et al. (2004) replicated the finding that, compared with HCs, schizophrenia patients showed lower GMR in the MDN and also found higher GMR in the pulvinar, the largest nucleus in the human thalamus. Lateral regions of the pulvinar have widespread projections, including connections with temporal association and visual and auditory cortices (Jones, 1985). Hazlett et al. found that dysfunction in thalamic nuclei with distinct cortical connections was associated with clinical symptom severity: lower GMR in the total thalamus, MDN, and pulvinar was associated with greater overall clinical symptoms; lower GMR in the pulvinar (with prominent temporal lobe connections) was associated with more *positive* symptoms; and lower GMR in the MDN (with prominent prefrontal cortex connections) was associated with more *negative* symptoms. Overall, this

work was novel as it extended prior structural MRI findings that showed thalamic nuclei reductions were more prominent in the left hemisphere, with MDN reduced only in schizophrenia patients, and pulvinar reductions in both schizophrenia and SPD groups compared with HCs (Byne et al., 2001).

Given the role of the MDN and pulvinar and their specific cortical connections, these findings were influential in supporting contemporary work that developed models where the multiple and diverse symptoms of schizophrenia reflect abnormalities in connectivity in the circuitry that links cortical regions (i.e. prefrontal and temporal cortex) and thalamic nuclei (e.g., Andreasen et al., 1998).

6. Temporal lobe

Inspired by lesion studies suggesting that dysfunction of the temporal lobe may be related to schizophrenia, DeLisi et al. (1989) conducted one of the initial examinations of temporal lobe GMR in unmedicated schizophrenia patients and HCs at NIMH. As was the case for most of the early studies conducted by this group, participants received brief electric shocks to their right forearm during the uptake period. Of note, a detailed anatomic delineation was employed, revealing that the patients demonstrated higher GMR in the left than right temporal lobe, and the increases in GMR compared with HCs were greatest in the anterior and superior temporal gyrus regions. In addition, the laterality finding was associated with clinical symptom severity. This work was among the first studies to suggest left-lateralized temporal lobe pathology in schizophrenia (Holinger et al., 1999). That is, while the lateralized results could have been attributable to the methodology employed (i.e. right-sided stimulation), a sizable body of literature using other forms of stimulation and/or behavioral assessment subsequently reported findings of left hemisphere abnormalities in individuals with schizophrenia. For example, several functional studies have shown left lateralization abnormalities in schizophrenia during language tasks, including the absence of left hemispheric dominance for phonological processing (Angrilli et al., 2009). Further, the aforementioned results from Delisi et al. (1989) also paved the way for today's large literature highlighting anomalies in superior temporal gyrus in schizophrenia and corresponding functional implications (e.g., auditory hallucinations, language deficits) (Barta et al., 1990).

Temporal lobe dysfunction was reported in other neuroimaging studies of schizophrenia (reviewed by Buchsbaum and Hazlett, 1998). For example, Hazlett et al. (2000) reported reduced GMR in temporal cortex regions (superior, middle, and inferior temporal gyrus) in schizophrenia patients compared with HCs during the SVLT uptake task. Among the patient group, greater use of a serial ordering strategy to remember the words (an inefficient strategy compared with semantic clustering) was associated with greater GMR in the right middle and inferior temporal gyrus, whereas, among the HCs, greater use of this inefficient strategy was associated with lower GMR in the frontal gyrus relative to the occipital lobe (i.e. greater hypfrontality). Taken together to this point, the early work of Buchsbaum and colleagues showed that impairments in function of the prefrontal and temporal cortex play a central role in the pathophysiology of cognitive dysfunction in the schizophrenia spectrum. This work was translational given animal studies of working memory implicated a cortical circuit involving the dorsolateral prefrontal, parietal, and temporal cortex, and thalamic regions in working memory (Goldman-Rakic, 1998), suggesting that disruption in an equivalent working memory circuitry in man may underlie the executive function or “strategy” failure observed in schizophrenia patients.

7. Cingulate gyrus

The cingulate gyrus is another key region implicated in the pathophysiology of schizophrenia, primarily due to its wide range of functionally distinct subdivisions, including the anterior and posterior cingulate. Upon examining this region and distinguishing cingulate subdivisions, Haznedar et al. (1997) revealed that, compared with HCs, unmedicated schizophrenia patients exhibited lower GMR in the anterior cingulate and higher GMR in the posterior cingulate while performing the CPT. These results not only extended prior reports of hypofrontality to include anterior limbic structures, they provided further support for the role of the cingulate in response selection.

Subsequently, using three-dimensional metabolic mapping, Haznedar et al. (2004) found that cingulate activity differed between schizophrenia and SPD during the SVLT uptake task. Compared with HCs, schizophrenia patients exhibited lower rGMR in the left anterior and right posterior cingulate, whereas SPD patients demonstrated higher metabolism in left posterior cingulate. However, overall cingulate GMR did not differ between the SPD and schizophrenia groups. These findings suggest that in contrast to controls, SPD patients employed unrelated association cortices to execute a working-memory task and possibly compensate for impaired function in the anterior cingulate.

8. Early PET studies examining seed-based functional connectivity

In the 1990s, Dr. Buchsbaum expanded on his work examining individual region-of-interest abnormalities in schizophrenia to begin focusing on potential “brain circuitry” abnormalities using correlational analyses of GMR data. In 1996, Buchsbaum and colleagues published the first study analyzing GMR inter-correlations in never-medicated schizophrenia patients (Katz et al., 1996). They found a series of abnormalities in cortical-subcortical circuitry in patients compared with HCs; the largest correlation between GMR in the anterior thalamus and the frontal cortex regions was where the groups differed the most, further implicating a thalamocortical circuitry abnormality in schizophrenia. Two years later, Buchsbaum et al. (1998) deployed a right putamen seed analysis using FDG-PET and reported positive correlations with frontal regions in HCs but not in schizophrenia, suggesting a frontostriatal functional connectivity deficit. Buchsbaum et al. (1999) then used a right caudate seed and found that the schizophrenia patients failed to show the same frontostriatal correlations that were observed in HCs. Subsequently, Mitelman et al. (2005) reported that unmedicated schizophrenia patients showed deficits in functional connectivity in the left hemisphere between the MDN and widespread frontotemporal cortical regions. This work was important as it further elucidated the role of the MDN in schizophrenia, implicating its connectivity with the frontotemporal cortex within the context of prior work reporting MDN metabolic and volumetric abnormalities (e.g., Byne et al., 2001; Hazlett et al., 2004; Kemether et al., 2003).

9. Examining individual differences and medication effects

The earliest brain imaging studies examining the effects of neuroleptics on glucose metabolism in schizophrenia took place at NIMH. These investigations examined patients when they were on and off neuroleptics. DeLisi et al. (1985b) reported that neuroleptic treatment was associated with an increase in mean cortical GMR but no significant change in anterior/posterior gradient. Temporal lobe glucose use relative to other cortical areas did not change significantly, although absolute glucose use in the left temporal lobe was greater in the medicated state. Additionally, both absolute and relative activity in the caudate nucleus was increased in the medicated state. Similar findings were reported by another group (Wolkin et al., 1985).

Buchsbaum et al. (1987) extended the visual identification methods of DeLisi et al. (1985b) by using a stereotaxic approach to identify the regions of interest. Buchsbaum et al. reported that basal ganglia GMR increased with medication, more in the putamen than in the caudate; however, similar to DeLisi et al. (1985b), the cortical anteroposterior ratio, an index of relative hypofrontality, was unaffected by neuroleptics (Buchsbaum et al., 1987).

Up until this point, prior studies were confounded by order effects, doctor's choice of neuroleptic medications and doses, and a lack of placebo-controlled and blinded ratings. The next investigation was a novel neuroimaging study in schizophrenia patients that involved a rigorous 10-week double-blind crossover trial of haloperidol/placebo and included FDG-PET scans at weeks 5 and 10 (Buchsbaum et al., 1992b). A novel and exciting aspect of this study included its examination of individual differences in treatment response to haloperidol, namely GMR in the caudate nucleus and putamen in clinical "responders" vs. "nonresponders." Buchsbaum et al. (1992b) found that GMR in the striatum was more closely related to clinical response than any other brain region. The patients who responded clinically showed the lowest GMR values in the striatum with placebo. Among the clinical "responders," haloperidol treatment had a "normalizing" effect on GMR in the striatum, i.e. the GMR while they were receiving haloperidol was higher than while they were receiving placebo. In contrast, the clinical "non-responders" showed no change in striatal GMR and a worsening of hypofrontality with haloperidol. Never-medicated schizophrenia patients were also found to have lower GMR in the ventral striatum compared to unmedicated patients (Shihabuddin et al., 1998; Shihabuddin et al., 2001). Taken together, these findings were critical precursors to current day treatment work, suggesting that schizophrenia patients who responded to haloperidol had an excess of dopamine receptors compared with those who were "nonresponders."

Later work compared the effects of second-generation antipsychotics like olanzapine and sertindole to the effects of haloperidol. Buchsbaum et al. (2007) reported that, while haloperidol increased striatal GMR and did not affect frontal GMR, olanzapine increased GMR in the frontal lobe more than in the occipital lobe, correcting the hypofrontality seen in FDG-PET studies of schizophrenia. While both medications increased thalamic GMR, haloperidol increased striatal GMR more so than olanzapine. In a 12-week double-blind crossover trial, schizophrenia patients received sertindole or haloperidol for 6 weeks and then received a FDG-PET scan and anatomical MRI (Buchsbaum et al., 2009). Patients were then crossed over to the other treatment and received a second set of scans at week 12. Patients were also compared with a group of unmedicated schizophrenia patients and a group of HCs. The main finding was that sertindole increased GMR in the dorsolateral prefrontal cortex (DLPFC) and lowered GMR in orbitofrontal cortex compared to haloperidol. Also, sertindole was associated with greater change toward HC values and was less similar to the values observed in the unmedicated comparison group for DLPFC gray matter and white matter underlying medial prefrontal and cingulate cortex. Buchsbaum concluded that the results were consistent with the sensorimotor adverse side-effect profile of sertindole and that second-generation antipsychotics like sertindole appeared to have greater frontal activation than first-generation antipsychotics like haloperidol. This early work examining brain activation changes following antipsychotic treatment was pivotal for future work using fMRI to examine individual differences in treatment response.

10. Conclusions

In this review, we revisited and paid tribute to the extensive early schizophrenia-spectrum work of Monte Buchsbaum and colleagues using FDG-PET. Buchsbaum is a pioneer in using FDG-PET to examine the neurobiology of schizophrenia-spectrum disorders and individual differences in treatment response. The FDG-PET work reviewed here was innovative and scholarly in numerous ways. These include, but are not limited to, the multi-methodological approach to precisely delineating brain regions of interest using structural MRI and FDG-PET together, the functional connectivity approaches, the inclusion of patients across the schizophrenia spectrum before SPD was considered to be a schizophrenia spectrum disorder in the DSM, and the recruitment of the world's largest sample sizes of unmedicated and never-medicated schizophrenia patients for functional neuroimaging to allow rigorous control for medication confounds. Since Dr. Buchsbaum's first FDG-PET studies of schizophrenia at NIMH in the 1980s, the development of fMRI has revolutionized the study of schizophrenia and accelerated the pace of discovery. Recent work using fMRI to examine thalamocortical connectivity (e.g., reviewed by Giraldo-Chica and Woodward, 2017) allows large-scale functional organization of the brain to be investigated. Progress in understanding the relationship between dysfunction in thalamocortical connectivity, particularly MDN connectivity, and clinical and cognitive symptom severity in the schizophrenia spectrum, remains a top priority.

Contributors

All authors were responsible for drafting parts of this review paper and approved the final version for publication. Dr. Hazlett was responsible for the overall format and content of the paper. Drs. Hazlett, Haznedar, and Goldstein all worked with and learned a tremendous amount about multimodal neuroimaging and more broadly, scientific inquiry from Dr. Buchsbaum during his tenure at UC Irvine and/or the Icahn School of Medicine at Mount Sinai.

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Conflicts of interest

The authors have no conflicts of interest to report.

Supplementary materials

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