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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