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Quantitative MRI measures of orbitofrontal cortex in patients with chronic schizophrenia or schizoaffective disorder

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Abstract

The relationship between orbitofrontal cortex (OFC) volumes and functional domains in treatment-resistant patients with schizophrenia or schizoaffective disorder is poorly understood. OFC dysfunction is implicated in several of the behaviors that are abnormal in schizophrenia. However, little is known about the relationship between these behaviors and OFC volumes. Forty-nine patients received magnetic resonance imaging scanning as part of a double-blind treatment study in which psychiatric symptomatology, neuropsychological function, and aggression were measured. OFC volumes were manually traced on anatomical images. Psychiatric symptomatology was measured with the Positive and Negative Syndrome Scale (PANSS). Aggression was measured with the Overt Aggression Scale (OAS) and with the PANSS. Neuropsychological function was assessed using a comprehensive test battery. Larger right OFC volumes were associated with poorer neuropsychological function. Larger left OFC gray matter volumes and larger OFC white matter volumes

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bilaterally were associated with greater levels of aggression. These findings are discussed in the context of potential iatrogenic effects.

Keywords: Orbitofrontal cortex; Schizophrenia; Aggression; Neuropsychological function

1. Introduction

The orbitofrontal cortex (OFC) plays a key role in several behaviors that are relevant to the psychopathology of schizophrenia. Damage to this region is associated with disinhibition, and impaired inhibition has been observed in neurocognitive measures (Garavan et al., 1999), as well as in aggression (Grafman et al., 1996) (see Hoptman, 2003, for a review) and substance abuse (Goldstein et al., 2001; Volkow et al., 1999). An important question is whether quantitative measures of OFC volumes are correlated with these behaviors in schizophrenia.

Numerous magnetic resonance imaging (MRI) studies have shown that volumes of several brain regions differ between patients with schizophrenia and healthy controls (see Niznikiewicz et al., 2003; Pearlson and Marsh, 1999; Shenton et al., 2001, for reviews). These structures include the ventricles, subregions of the frontal and temporal lobes, and subcortical structures including the basal ganglia, corpus callosum, thalamus, and possibly the cerebellum. In addition, many of these studies have found that regional parenchymal volumes, such as medial temporal and inferior parietal regions, are larger in healthy controls than in patients with schizophrenia.

However, the reverse is also found, especially in the basal ganglia. The enlargement of basal ganglia volumes in patients with schizophrenia was initially described in MRI studies by DeLisi et al. (1991) and Jernigan et al. (1991). This relationship appears to vary with treatment history. Patients with schizophrenia who had been treated with typical antipsychotic drugs (APD) showed increases in the volume of the caudate (Chakos et al., 1994). Typical APDs were also associated with a similar, though statistically nonsignificant, enlargement of cortical volumes. Similar results for caudate volumes were found by Keshavan et al. (1994). Overall, a substantial majority of the MRI studies on the caudate have shown increased volumes in schizophrenia (Shenton et al., 2001).

In a postmortem study in rats, chronic treatment with haloperidol was associated with increased striatal volumes (Chakos et al., 1998). This result indicates that the effect of haloperidol on striatal volumes is not entirely secondary to the pathophysiology of schizophrenia. In further support of this argument, when patients were switched to clozapine, an atypical APD, caudate volumes were reduced (Chakos et al., 1995; Frazier et al., 1996). Thus, the increase in caudate volumes may reflect an iatrogenic effect of typical APD treatment.

The type of APD medication administered will almost certainly vary with the duration of illness, given that the oldest of the atypicals, clozapine, was only given FDA approval in 1989. Thus, older patients have received considerable exposure to typical APDs. Consistent with this notion, Lang et al. (2001) found that basal ganglia volumes were larger in patients who had received at least 12 weeks of continuous typical APD treatment than in first-episode patients. Moreover, the correlation between globus pallidus volume and length of typical APD treatment approached significance ($r=0.56$, $P=0.06$).

The implications of these findings may extend to other regions of the brain as well, as suggested also by the data published by Chakos et al. (1994) and by Benes et al. (1985a,b), who found increased neuronal soma volumes in the striatum and medial prefrontal cortex in rats treated with haloperidol. It is therefore reasonable to suggest that such volumetric effects might be found in regions other than the basal ganglia. This issue is important in a region such as the OFC that plays a key role in functions that are impaired in schizophrenia.

The findings of Arango et al. (2003) appear to be particularly relevant in this regard. They found that patients with larger prefrontal brain volumes were more likely to benefit from clozapine treatment.