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Unchanged packing density but altered size of neurofilament immunoreactive neurons in the prefrontal cortex in schizophrenia and major depression

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Abstract

Morphometric changes in the general population of Nissl-stained neurons in area 9 of the dorsolateral prefrontal cortex have been reported in major depressive disorder (MDD) and schizophrenia. These alterations include lamina-specific reductions in the packing density of neuronal somata in MDD, increases or reductions in the density of neuronal somata in schizophrenia, and reductions in average size of neuronal somata in both MDD and schizophrenia. These changes are prominent in deep layer III, where pyramidal excitatory neurons establishing cortico-cortical association connections are localized. To test whether deep layer III pyramidal neurons are differentially affected in MDD or schizophrenia, an antibody was used that labels both phosphorylated and non-phosphorylated forms of the 200 kD neurofilament protein (NF200) in pyramidal cells of layer III in area 9. The packing density and somal size of NF200-immunoreactive (IR) pyramidal neurons were measured in area 9 in 13 subjects with nonpsychotic MDD, 11 subjects with schizophrenia and 13 psychiatrically normal controls. Analysis of covariance did not reveal a difference in packing density among groups. However, the mean size of NF200-IR somata was significantly larger in subjects with schizophrenia than in controls. These results indicate that this neuronal subpopulation does not contribute to the smaller average size of neuronal somata in layer III of prefrontal cortical area 9 in schizophrenia or MDD. In addition, the enlarged somal size in schizophrenia as compared to controls suggests that NF200 neurons may contribute differentially to unique cognitive disturbances present in schizophrenia and not in MDD subjects.

Keywords: Postmortem; Immunohistochemistry; Brodmann's area 9; Human; Psychiatry

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1. Introduction

In major depressive disorder (MDD) and schizophrenia both structural and functional neuroimaging studies reveal similar alterations in the volume and metabolic activity of the human dorsolateral prefrontal cortex (dlPFC) (Goodwin, 1997; Kennedy et al., 1997; Steffens and Krishnan, 1998; Sweeney et al., 1998; Henn and Braus, 1999; Lim et al., 1999; McCarley et al., 1999; Drevets, 2000; Manoach et al., 2000). Histopathological research using a Nissl-stain to identify virtually all neurons demonstrates that these alterations include lamina-specific reductions in the packing density of neuronal somata in MDD, lamina-dependent alterations of neuronal density in schizophrenia, and reductions in neuronal size in both MDD and schizophrenia (Selemon et al., 1995; Rajkowska et al., 1998; Selemon et al., 1998; Rajkowska et al., 1999; Cotter et al., 2001). These changes are prominent in deep cortical layer III (sublayers IIIb and IIIc), the site of many pyramidal excitatory neurons establishing long range cortico-cortical connections (Carmichael and Price, 1995; Kritzer and Goldman-Rakic, 1995; Barbas and Rempel-Clower, 1997; Barbas, 2000; Cavada et al., 2000). Pyramidal neurons also receive projections from neurons of the mediodorsal nucleus of the thalamus (Barbas, 2000), and these thalamic cell bodies appear to be reduced in number in some (Pakkenberg, 1990; Popken et al., 2000; Byne et al., 2002) but not all (Cullen et al., 2003) studies of schizophrenia. The connection pattern in deep cortical layer III pyramidal neurons suggests that pathological changes may occur in these pyramidal cells that are associated with psychiatrically-relevant dysfunction of prefrontal circuits. In addition, since some of the cognitive anomalies in MDD differ from those in schizophrenia, there may be disease-specific differences in the pathology of area 9 pyramidal neurons and the corresponding circuits in which these cells are involved. In particular, the average neuronal soma size is significantly reduced in sublayers b and c of layer III in cortical area 9 of subjects with schizophrenia (Rajkowska et al., 1998). An independent study found a similar reduction in the size of pyramidal neurons in deep layer III of area 9 in schizophrenia (Pierri et al., 2001). In contrast, in MDD there is no significant change in average neuronal soma size in sublayers IIIb and IIIc, and the average neuronal soma size was significantly decreased only for the undivided layer III (Rajkowska et al., 1999). Furthermore, the density of the largest neuronal somata in layer III, which mainly correspond to pyramidal cells located in sublayer IIIc, is significantly reduced in MDD (Rajkowska et al., 1999). The above data in postmortem tissue suggest that changes in specific populations of pyramidal cells in cortical layer III may be differentially involved in the pathophysiology of schizophrenia and depression.

A specific population of deep layer III pyramidal neurons with long cortico-cortical projections has been detected in the dlPFC of humans and other primates using antibodies raised against the various protein subunits of neurofilaments (Hof et al., 1995, 1996; Nimchinsky et al., 1996; Hof et al., 2000). For example, in Alzheimer's disease (AD), the packing density of this neuronal subpopulation is dramatically reduced (Hof et al., 1990) and this loss is likely to contribute to the severe cognitive deficits displayed by AD patients. Since cognitive dysfunction is prominent among the psychiatric symptoms of schizophrenia patients, Pierri et al. (2003) assessed the changes in somal size and packing density of the same population of neurons in schizophrenia by using an antibody specific for the non-phosphorylated 160 and 200 kD subunits of neurofilaments (Pierri et al., 2003) and the three-dimensional optical disector probe. This immunohistochemical study, in contrast to the morphometry studies based on Nissl-staining (Rajkowska et al., 1998; Pierri et al., 2001) using the same stereological principles, did not find significant changes in the packing density or size of specifically labeled pyramidal neurons in the left hemisphere in subjects with schizophrenia (Pierri et al., 2003). Interestingly, in the study by Pierri et al. (2003), the group of subjects with schizophrenia included four schizoaffective subjects, while some of the previous studies of the general population of pyramidal cells identified with Nissl-staining did not include schizoaffective subjects (Rajkowska et al., 1995; Selemon et al., 1998). In addition, the antibody used by Pierri et al. (2003) does not recognize the phosphorylated forms of neurofilaments, raising the possibility that labeling with antibodies that detect both phosphorylated and non-phosphorylated forms of neurofilaments may still