How dorsal prefrontal cortex (PFC) neuronal pathology in schizophrenia might be reflected in neuroimaging studies of schizophrenic patients (SCZ) remains an area of active debate. One potential confound is that dorsal and ventral PFC are often grouped together under general labels (‘hypofrontality’) applied to putative physiological abnormalities of PFC function identified by imaging studies. In healthy subjects, there is growing evidence for a functional distinction between dorsal ‘executive’ (e.g., manipulation or inhibition) and ventral (maintenance) PFC subregions in the context of cognitive operations like working memory (WM). We looked for such a distinction in the fMRI response to varying WM load in SCZ and matched controls using the n-back WM task. We concurrently collected an independent in-vivo measure of neuronal pathology using 1H-MRSI (n-acetylaspartate or NAA measures). We found a distinction between dorsal and ventral PFC in their fMRI response to varying WM load and also in the relationship of these responses to WM performance and NAA measures. While both dorsal and ventral PFC fMRI responses were abnormal, only the dorsal PFC response differed from controls in all three analyses. In particular, the magnitude of the abnormal response in dorsal PFC was the only regional fMRI response predicted by the magnitude of PFC pathology in SCZ (i.e., PFC NAA measures). These data suggest that there is greater impairment of dorsal v. ventral PFC function in SCZ and that a failure to appropriately modulate activity within dorsal PFC may be the most germane physiological signature of PFC neuronal dysfunction in SCZ.

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