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Associated Microscale Spine Density and Macroscale Connectivity Disruptions in Schizophrenia

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ABSTRACT

BACKGROUND: Schizophrenia is often described as a disorder of dysconnectivity, with disruptions in neural connectivity reported on the cellular microscale as well as the global macroscale level of brain organization. How these effects on these two scales are related is poorly understood.

METHODS: First (part I of this study), we collated data on layer 3 pyramidal spine density of the healthy brain from the literature and cross-analyzed these data with new data on macroscale connectivity as derived from diffusion imaging. Second (part II of this study), we examined how alterations in regional spine density in schizophrenia are related to changes in white matter connectivity. Data on group differences in spine density were collated from histology reports in the literature and examined in a meta-regression analysis in context of alterations in macroscale white matter connectivity as derived from diffusion imaging data of a (separately acquired) group of 61 patients and 55 matched control subjects.

RESULTS: Densely connected areas of the healthy human cortex were shown to overlap with areas that display high pyramidal complexity, with pyramidal neurons that are more spinous ($p = .0027$) compared with pyramidal neurons in areas of low macroscale connectivity. Cross-scale meta-regression analysis showed a significant association between regional variation in level of disease-related spine density reduction in schizophrenia and regional level of decrease in macroscale connectivity (two data sets examined, $p = .0028$ and $p = .0011$).

CONCLUSIONS: Our study presents evidence that regional disruptions in microscale neuronal connectivity in schizophrenia go hand in hand with changes in macroscale brain connectivity.

Keywords: Connectivity, Connectome, Diffusion imaging, MRI, Schizophrenia, Spine density

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Schizophrenia has a long history of being hypothesized as a disorder of dysconnectivity. Pioneering neuroanatomists and psychiatrists Meynert, Kraepelin, and Wernicke suggested that dysconnectivity of association pathways may constitute a core aspect of the etiology of schizophrenia; contemporary theories have hypothesized that affected brain connectivity and network organization play an important role in the disruption of integrative brain processes in patients with schizophrenia (1,2).

Dysconnectivity theories have been supported by empirical findings at the microscale and the macroscale levels of brain organization. Histologic examinations reported reduced spine density (3–5) and affected morphology (6,7) of neurons in several frontal and temporal brain areas. These microscale alterations have been suggested to be localized to pyramidal neurons of layer 3 of the cerebral cortex (see Discussion) (8,9), a cortical layer known to play an important role in long-range cortico-cortical connectivity and region-to-region communication (10). At the macroscale level of brain organization, neuroimaging studies reported that schizophrenia includes disruptions of cortical structure and white matter connectivity (1,11–15). Advances in diffusion-weighted imaging (DWI) techniques have led to emerging evidence that disrupted macroscale brain network organization plays an important role in the disorder (14,16–21). However, how these disease effects at these two scales of brain organization are related is poorly understood.

In this study, we present potential evidence that disease-related alterations in spine density of pyramidal neurons in schizophrenia are associated with changes in inter-areal connectivity at the macroscale level of brain organization. In part I of the study, we report an examination of a microscale-macroscale (micro-macro) relationship in the healthy human brain, collating quantitative data on layer 3 spine density of cortical regions from histologic examinations reported in the literature and cross-referencing the data with data on regional macroscale connectivity as derived from magnetic resonance imaging (MRI). Next, in part II of our study, we continued our examination by studying a possible link between disease-related changes in spine density of cortical regions and changes in macroscale connectivity as derived from MRI analysis. We collated data from the literature on group differences in reductions in spine density in schizophrenia as measured by histologic examinations, and we cross-referenced

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this microscale data in a meta-regression analysis with data on macroscale dysconnectivity effects as derived from analysis of high-resolution diffusion MRI data of a (separate) group of 61 patients with chronic schizophrenia and 55 matched healthy control subjects. Using meta-regression analysis, we present evidence of neural dysconnectivity at the microscale and macroscale levels of brain organization in schizophrenia to be potentially related.

METHODS AND MATERIALS

Part I: Micro-Macro Relationship in the Healthy Brain

Microscale Data. Data on cortical variation of pyramidal layer 3 spine density in the healthy brain were collated across studies found in the literature (Supplemental Table S1) (3,22–26). With studies using different methodologies (Golgi, Golgi-Cox, rapid Golgi) (Supplemental Table S2), data were standardized across studies (taking the data of the Jacobs group as a reference) to allow across-study comparison (Supplement).

In addition to spine density, the studies of the Jacobs group (Supplemental Table S1) (22,24,25) reported quantitative data on total length of the dendritic tree, total number of dendritic segments, total mean segment length of a dendritic branch, and total estimated spine count (Figure 1A). These additional data were collated (Supplemental Table S1) and examined in the context of regional variation of macroscale connectivity (see later).

In total, across these 6 studies, data on pyramidal complexity were collected at 14 different sites of the cortex (Figure 1C). The spatial locations of the cortical patches were mapped to corresponding cortical regions of the cortical Desikan-Killiany atlas used for DWI connectome reconstruction (Figure 1C and Supplemental Table S1).

Macroscale Connectome Reconstruction and Analysis. A macroscale human connectome map of 114 cortical regions was derived from streamline tractography of high-resolution DWI data from the Human Connectome Project (Q3, $N = 215$ subjects) (see Supplement for details) (27). A group-averaged structural connectivity matrix was formed by taking

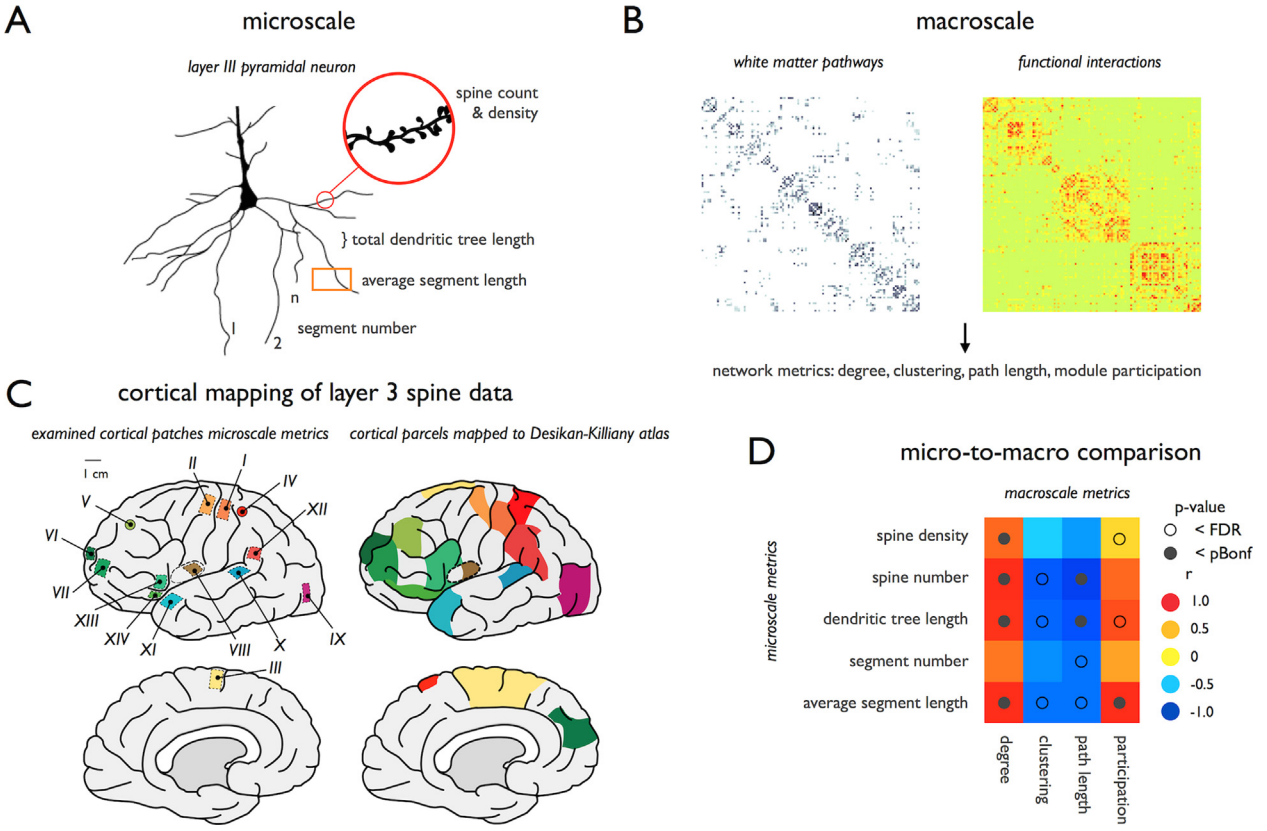

Figure 1. **(A)** Collated data on microscale layer 3 pyramidal neurons involved five metrics of dendritic pyramidal structure. **(B)** Macroscale data involved reconstruction of corticocortical anatomic pathways by means of diffusion magnetic resonance imaging (left matrix) and the reconstruction of functional connectivity (right matrix) derived from resting-state functional magnetic resonance imaging recordings of Human Connectome Project data. **(C)** The 14 cortical patches (regions I–XIV) (Supplemental Table S1) from which data on layer 3 pyramidal complexity were collated from the literature. For 12 regions, the approximate size of the examined cortical patch was reported in the original article (shown as patches); for 2 regions (shown as dots), this information was absent. Roman numerals correspond to the region descriptions in Supplemental Table S1. Right panel shows the corresponding selected cortical parcels of the Desikan-Killiany atlas. **(D)** 5 × 4 correlation matrix of the five microscale and four macroscale network metrics. open circles, trend-level correlations surviving false discovery rate (FDR); closed circles, correlations surviving more strict partial Bonferroni correction (pBonf). Visual representations of pyramidal dendritic tree are based on Anderson *et al.* (22).