Tract-specific white matter hyperintensities and neuropsychiatric syndromes: a multi-center memory clinic study

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ABSTRACT

Background

White matter hyperintensities (WMH) have been implicated in the pathogenesis of neuropsychiatric symptoms of dementia but the functional significance of WMH in specific white matter (WM) tracts is unclear. We investigate whether WMH burden within major WM fiber classes and individual WM tracts are differentially associated with different neuropsychiatric syndromes in a large multicenter study.

Methods

Neuroimaging and neuropsychiatric data of seven memory clinic cohorts through the Meta VCI Map consortium were harmonized. Class-based analyses of major WM fibers (association, commissural, projection) and region-of-interest-based analyses on 11 individual WM tracts were used to evaluate associations of WMH volume with severity of hyperactivity, psychosis, affective, and apathy syndromes.

Results

Among 2935 patients (50.4% female; mean age=72.2 years; 19.8% subjective cognitive impairment, 39.8% mild cognitive impairment, 40.4% dementia), larger WMH volume within projection fibers (B=0.24, SE=0.10, p=0.013) was associated with greater apathy. Larger WMH volume within association (B=0.31, SE=0.12, p=0.009), commissural (B=0.47, SE=0.17, p=0.006) and projection (B=0.39, SE=0.16, p=0.016) fibers were associated with greater hyperactivity, driven by the inferior fronto-occipital fasciculus (B=0.50, SE=0.18, p=0.006), forceps major (B=0.48, SE=0.18, p=0.009) and anterior thalamic radiation (B=0.49, SE=0.19, p=0.011), respectively. Larger WMH volume in the uncinate fasciculus (B=1.82, SE=0.67, p=0.005) and forceps minor (B=0.61, SE=0.19, p=0.001) were additionally associated with greater apathy. No associations with affective and psychosis were observed.

Conclusions

Tract-syndrome specificity of WMH burden with apathy and hyperactivity suggests that disruption of strategic neuronal pathways may be a potential mechanism through which small vessel disease affects emotional and behavioral regulation in memory clinic patients.

Key Messages

What is already known on this topic

The impact of white matter hyperintensities (WMH) in individual white matter tracts is suggested to have functional differentiation in cognitive impairment but their influence on neuropsychiatric symptoms (NPS) is unclear. This study evaluates tract-specific WMH burden with different neuropsychiatric syndromes.

What this study adds

This study uncovers tract-syndrome associations of WMH volume within major white matter fiber classes and specific white matter tracts with apathy and hyperactivity syndromes, providing insights into potential neurobiological projections underlying emotional and behavioral dysregulation in memory clinic patients.

How this study might affect research, practice or policy

Our findings support the research utility of quantifying WMH at the level of specific white matter tracts to understand how disruption of strategic neuronal pathways may affect NPS in older adults.

INTRODUCTION

Neuropsychiatric symptoms (NPS) are highly prevalent in people with dementia,[1] indicating that these non-cognitive symptoms constitute a core clinical feature of the disease process. Most NPS develop progressively from preclinical or mild cognitive impairment (MCI) stages[2] and these behavioral and psychological disturbances may occur in more than 90% of individuals with dementia.[3] The associations of greater neuropathology with both increased severity of dementia and neuropsychiatric manifestation suggest an etiological commonality driven by underlying neural dysfunction.[2]

In particular, the role of white matter hyperintensities (WMH) of presumed vascular origin as the neurobiological substrate of NPS has been widely examined. A higher burden of global WMH has been found to be associated with more severe depression,[4 5] apathy,[4 6] and increased hyperactive symptoms.[7] However, a recent systematic review and meta-analysis found that there remains substantial inconsistency in the relationship between global WMH burden and NPS.[8] In addition, as the distribution of WMH varies between individuals and white matter is known to have a functional differentiation rather than a bulk substance,[9] global measures of WMH may have limited usefulness in determining the impact of inter-individual differences in WMH burden on NPS. This is further complicated by the presence of substantial heterogeneity in the clinical manifestation of NPS. Therefore, elucidating the relationships between the location of white matter lesions and different neuropsychiatric presentations could provide a finer understanding of the clinical impact of strategic WMH on NPS.

Emerging evidence demonstrates that WMH in tract-defined classes of white matter fiber bundles (i.e. association, commissural, projection)[10] and individual white matter tracts have differential impact on cognitive impairment.[11-13] Beyond cognitive function, WMH localization in bilateral anterior thalamic radiation has been associated with more severe apathy in a small sample of patients with MCI[14] and greater WMH volume in the forceps minor and

corticospinal tracts in association with greater self-reported depressive symptoms in patients with vascular brain injury.[15] While these initial studies support the utility of quantifying WMH at the level of specific white matter tracts to understand their impact on neuropsychiatric manifestation, less is known about the effects of WMH within tract-defined classes on NPS. The disruption of strategic white matter pathways may be a key mechanism through which small vessel disease (SVD) affects not only cognition, but also the regulation of mood and behavior.

In the current study, we analyzed tract-specific WMH to gain additional insights into the role of strategic WMH on neuropsychiatric impairment in a large multicenter memory clinic sample. Leveraging on a large sample size of our multi-center study with harmonized individual participant data and greater lesion coverage, we aim to elucidate how WMH burden within the three classes of white matter fibers and in individual white matter tracts are differentially associated with different neuropsychiatric syndromes (i.e. hyperactivity, psychosis, affective, and apathy).

METHODS

Study participants

This study analyzed data from a previously published Meta VCI Map consortium project in memory clinic patients.[13] The Meta VCI Map consortium aims to examine the clinical impact of vascular lesions by performing meta-analyses on strategic lesion locations for vascular cognitive impairment using lesion-symptom mapping (https://metavcimap.org).[16] The full dataset involved individual patient data from 3,525 patients from 11 memory clinic cohorts (Figure S1). Eligibility criteria for the previously published study were: (1) patients who were evaluated with cognitive complaints at an outpatient clinic; (2) available MRI with T1 and T2 or FLAIR images; (3) available clinical and neuropsychological data. Patients

diagnosed with subjective cognitive impairment (SCI), MCI, or dementia of vascular, neurodegenerative, or mixed etiologies were included. Patients diagnosed with cognitive impairment due to non-vascular or non-neurodegenerative causes (e.g. brain tumor, traumatic head injury, multiple sclerosis, substance or alcohol abuse, primary psychiatric disorders), or monogenic etiology (e.g. CADASIL, presenilin mutations) were excluded. The exclusion criteria of each cohort are published elsewhere.[13] Final cohorts (N = 2935 from 7 cohorts) for the present study were included based on the additional availability of neuropsychiatric data (Figure S1). Central data processing and analysis were conducted at the University Medical Center Utrecht, the Netherlands.

Standard protocol approvals, registrations, and patient consents

Ethical and institutional approval and written informed consent for data collection and data sharing were obtained by all cohorts following their respective local regulations.

Evaluation of neuropsychiatric syndromes

NPS were assessed using the Neuropsychiatric Inventory (NPI)[17] in five cohorts (N = 1,393) and NPI Questionnaire (NPI-Q) in two cohorts (N = 1,542).[18] Both instruments are caregiver-based and retrospectively capture the presence and severity of 12 specific behavioral and psychological symptoms: delusions, hallucinations, agitation, anxiety, depression, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, nighttime behavior, and appetite/eating behavior. Both the NPI and NPI-Q assess for the severity (1 - 3) of each symptom while the NPI additionally assesses for the frequency (1 - 4). Although frequency and severity ratings are highly correlated, symptom severity has been found to be more strongly associated with caregiver distress than symptom frequency.[18] The severity ratings of all participants were harmonized for the current analysis, such that the total severity score represents the sum of individual symptom severity scores, ranging from 0 to 36.

We further classified the 12 individual symptoms into four neuropsychiatric syndromes that were previously derived using principal component analysis by the European Alzheimer's Disease Consortium.[19] The hyperactivity syndrome comprised of agitation, euphoria, disinhibition, irritability, and aberrant motor behaviors; psychosis syndrome comprised of delusion, hallucination, and nighttime behaviors; affective syndrome comprised of anxiety and depression; and apathy syndrome comprised of apathy and appetite/eating behavior. This classification is widely used[7 20 21] and has been replicated in European[22] and multi-ethnic Asian populations.[20]

Neuroimaging data processing and harmonization

WMH quantification. Segmentation of lesions was performed using T2-FLAIR images. Segmentations for ACE and UMCC were performed in Utrecht using an established technique as described previously[13] while segmentations for the remaining cohorts were provided by the respective centers.

Generation of WMH maps. The full registration procedure is described in detail in the Supplementary Material of prior work.[13] Briefly, the T2-FLAIR images were first registered to the corresponding T1 images via linear registration using the established elastix toolkit.[23] Next, the T1 images were registered to the T1 Montreal Neurological Institute (MNI)-152 brain template using linear and non-linear registration. The results of the registration were subsequently composed into a single transform and the final composed transform was applied to the binary WMH mask for spatial normalization[24] (the source code of our registration workflow can be found on https://github.com/Meta-VCI-Map/RegLSM). An age-specific template in MNI space was used to improve registration quality. Both ADNI and AUCD provided WMH maps that were already registered to the MNI-152 space using in-house processing pipelines. Visual inspection was also performed to ensure overall lesion data quality and minor manual modifications were made where necessary.[12 13]

Quantification of tract-defined WMH. Two approaches (Region-of-interest (ROI) based and class-based) were used to quantify tract-defined WMH. To evaluate the impact of lesion volume in predefined white matter tracts on NPS, 20 major white matter tracts were generated using the John Hopkins University (JHU)-atlas with a 10% probability threshold.[25] Of which, eighteen bilateral white matter tracts were merged to create nine ROIs. In addition to forceps major and forceps minor, a total of 11 ROIs were generated for analysis. To evaluate how WMH within the three major classes of white matter fiber bundles (association, commissural, projection) were differentially associated with NPS, the WMH volumes of each tract were extracted and summed according to the class of fiber bundles (Figure 1). The association tract class consisted of the cingulum-cingulate gyrus, cingulum-hippocampus, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, superior longitudinal fasciculus, superior longitudinal fasciculus temporal part, and uncinate fasciculus. The commissural tract class consisted of the forceps major and forceps minor. The projection tract class consisted of the anterior thalamic radiation and corticospinal tract. Log transformation ($\log^{10}$*(WMH volume+1)) was performed for WMH volumes of all ROIs and tract classes to adjust for data skewness.

Computation of brain parenchymal fraction. As a measure of whole brain atrophy, the brain parenchymal fraction (BPF)[26] of each subject was calculated using the Computational Anatomy Toolbox for SPM12 (https://neuro-jena.github.io/cat/).[27] The BPF for ADNI and AUCD cohorts were computed using an automated extraction method as described previously.[28 29]

Statistical analyses

Chi-squared test was used to explore differences in the prevalence of neuropsychiatric syndromes as a function of clinical diagnosis (SCI, MCI, and dementia) and further post-hoc tests were performed for statistically significant differences. Linear mixed models were used

to investigate whether greater WMH volume within each class of white matter fibers and individual ROI was associated with higher neuropsychiatric syndrome severity scores. The models were adjusted for age, sex, diagnosis as fixed effects, and study site as random effect. Further adjustment for BPF was performed to determine whether these effects were robust, even after accounting for global neurodegeneration. Lastly, we tested for interactions between WMH volume and diagnosis in all models to determine if the associations of WMH volume with neuropsychiatric severity scores were influenced by degree of cognitive impairment. Total WMH was not added as a covariate in these models to prevent multicollinearity. For all linear mixed models, *p*-values were additionally corrected for multiple testing at a false discovery rate (FDR) of $q < 0.05$ for three classes of white matter fibers or 11 ROIs.

RESULTS

Participant characteristics

Four cohorts without neuropsychiatric data were excluded from the analysis (Figure S1), leaving a total of 2,935 participants (mean age = 72.2 ± 8.4 years; 50.4% female; 19.8% SCI, 39.8% MCI, 40.4% dementia) from seven eligible cohorts: Austria (PRODEM); the Netherlands (ACE, TRACE-VCI, UMCC); Singapore (Harmonization); and the USA (ADNI (http://adni.loni.usc.edu), AUCD) (Table 1). The characteristics of the individual cohorts are summarized in Table S1.

In this study, 69.6% of participants reported a presence of NPS (NPI score ≥ 1; 49.6% in SCI, 63.7% in MCI, 85.3% in dementia). The most common neuropsychiatric syndrome was hyperactivity (46.7%), followed by affective (40.1%), apathy (38.1%), and psychosis (29.2%). The hyperactivity syndrome was driven by the irritability symptom, while depression, apathy, and nighttime behavior were most frequent within affective, apathy, and psychosis syndromes, respectively (Figure 2). The presence of all syndromes was more common in patients with

dementia compared to MCI and SCI participants while MCI patients tended to have more affective, apathetic, and hyperactive symptoms compared to SCI participants (Table S2).

Class-based WMH and Neuropsychiatric Syndromes

Larger WMH volume within the class of projection fibers (B = 0.24, SE = 0.10, p = 0.013), but not association (B = 0.11, SE = 0.07, p = 0.116) or commissural fibers (B = 0.10, SE = 0.10, p = 0.340), was associated with higher apathy severity scores, which remained significant after further adjustment for BPF (Table 2). Larger WMH volume within all classes of association fibers (B = 0.31, SE = 0.12, p = 0.009), commissural fibers (B = 0.47, SE = 0.17, p = 0.006), and projection fibers (B = 0.39, SE = 0.19, p = 0.011) were associated with higher hyperactivity severity, independent of BPF (Table 2). All associations remained significant after FDR correction for multiple testing ($q < 0.05$). No significant associations between class-based WMH volume and affective or psychosis syndrome scores were observed (Table 2). There was no significant interaction ($p > 0.05$) between class-based WMH volume and diagnostic group in all models.

ROI-based WMH and Neuropsychiatric Syndromes

Larger WMH volume in the uncinate fasciculus (B = 1.82, SE = 0.67, p = 0.005) and forceps minor (B = 0.61, SE = 0.19, p = 0.001) were associated with higher apathy severity scores. Larger WMH volume in the inferior fronto-occipital fasciculus (B = 0.50, SE = 0.18, p = 0.006), forceps major (B = 0.48, SE = 0.18, p = 0.009), and anterior thalamic radiation (B = 0.49, SE = 0.19, p = 0.011) were associated with higher hyperactivity severity scores. These associations remained significant after FDR correction for multiple comparisons and were independent of BPF (Table 3). No significant associations between tract-specific WMH volume and affective or psychosis syndrome scores were observed. There was also no significant interaction ($p > 0.05$) between WMH volume and diagnostic group in all models.

DISCUSSION

This large multicenter study characterizes the neuropsychiatric profile of tract-defined WMH in memory clinic patients. We identified significant associations of larger WMH volume with greater severity of apathy and hyperactivity syndromes, but not with affective and psychosis syndromes. The associations of WMH with apathy syndrome were found within the projection fibers and in specific tracts of the uncinate fasciculus and forceps minor. In contrast, widespread associations of greater WMH with hyperactivity syndrome were found within all three classes of association, commissural, and projection fibers. The strongest associations were found in the inferior fronto-occipital fasciculus, forceps major, and anterior thalamic radiation, respectively. These results suggest that the impact of WMH on neuropsychiatric syndromes may depend on the location of pathology, with specific tract-syndrome relationships that are particularly evident for apathy and hyperactivity syndromes.

Consistent with previous reports, caregivers of dementia patients reported the highest presence across all symptoms as compared to MCI or SCI patients.[1 3] We also observed significant differences between MCI and SCI in the rates of hyperactive, affective, and apathy syndromes that were often associated with progressive cognitive decline.[30] The increased rate of NPS across disease stages is also consistent with increasing severity of neuropathology across the dementia spectrum, particularly with higher WMH burden in earlier disease stages.[31]

Within the association fibers, the association of greater WMH with hyperactivity was strongest in the inferior fronto-occipital fasciculus, one of the longest fiber tracts that integrates auditory and visual cortices with the prefrontal cortex.[32] The inferior fronto-occipital fasciculus was found to be involved in peripheral vision and visuospatial information processing including facial emotions,[33] and has been implicated in greater deficits in executive function and language.[13] Hence, WMH in the inferior fronto-occipital fasciculus resulting in disruption

to cross-network of cognitive control may contribute to the occurrence of emotional dysregulation and disinhibition associated with hyperactive disturbances. In contrast, the association of greater WMH with apathy was found in the uncinate fasciculus that connects the frontal and temporal lobes via the amygdala.[32] Traditionally considered as part of the limbic system, the uncinate fasciculus may play an important role in attaching emotional salience to visual information, regulating emotional responses to auditory stimuli, and supporting emotion-associated cognitive tasks.[33] Disruption of the uncinate fasciculus resulting in emotional dysregulation may be a potential pathway for impaired motivated behaviors that is central to the apathy syndrome.

In the commissural tracts that primarily integrate sensory, motor, and higher-order cognitive information from both hemispheres,[34] we found that greater WMH in the forceps major, that provides connection between the occipital lobes was associated with greater hyperactivity, while greater WMH in the forceps minor, that connects both frontal cortices was associated with greater apathy. Based on their topographical organization, the forceps major supports transfer of somatosensory information in posterior regions while the forceps minor support the processing of higher cognition and emotional functions anteriorly,[34] complementary to the strategic association tracts for hyperactivity and apathy respectively. Although not much is known about the neuropsychiatric impact of WMH in these specific tracts in dementia, a review of studies has found a common reduction of white matter integrity within these tracts in patients with major psychiatric disorders.[35] Previously, it had also been found that WMH burden within the inferior fronto-occipital fasciculus was associated with reduced functional connectivity in tract-connected default mode network in Alzheimer's disease.[36] The default mode network has been linked with processing of affective valence and arousal and may be an important brain network for constructing discrete emotional experience.[37] Together, this evidence suggests that differential microstructural damage of white

matter pathways or disrupted neural circuitry involved in the integration of cognition and emotion in the commissural tracts (i.e. forceps major for hyperactivity and the forceps minor for apathy) may be potential mechanisms underlying strategic WMH and these neuropsychiatric dysfunctions.

Beyond these differences between apathy and hyperactivity, both syndromes were associated with greater WMH within the projection fibers, which consist of tracts that interconnect cortical areas with the deep nuclei and cerebellum, brainstem, and spinal cord.[32] These nuclei are responsible for producing neurotransmitters such as serotonin, noradrenaline, and dopamine, which have been implicated in mood and behavioral changes in dementia.[38 39] Studies have found that WMH in the projection tracts was associated with poorer memory, attention, and executive functioning.[10 13] Specifically, the anterior thalamic radiation consists of projections from the anterior thalamic nuclei to the anterior cingulate cortex, which is known to be critical for emotion-motivational functions in AD.[40] One previous study has found that WMH in the anterior thalamic radiation is associated with apathy but not with other NPS in a small sample of MCI patients.[14] Impaired white matter integrity within the anterior thalamic radiation was also associated with deficits in emotional regulation and motivated behaviors.[41] Hence, WMH-associated apathetic and hyperactive manifestations in the projection tracts may signify a common disruption of cortico-subcortical neural pathways with neurochemical changes sub-serving complex human behaviors.

We did not identify any strategic localization of WMH for psychosis. In contrast to more radiologically observable white matter disease such as WMH, some evidence suggest that psychotic disorders may be more associated with other changes in white matter, possibly induced by cellular dysfunction resulting in degraded white matter integrity and cerebral dysconnectivity.[42] Others have found that psychotic symptoms were involved in neurodegenerative pathologies such as increased cortical atrophy[43] and abnormal dopamine

receptor function on positron emission tomography imaging.[44] We also did not find any associations of tract-defined WMH with affective syndrome to support previous finding that WMH in the corticospinal tract and forceps minor were modestly associated with self-reported depressive symptoms, especially in patients with SCI.[15] Taken together, the contribution of vascular brain injury to affective syndromes is likely complex, heterogeneous, and dependent upon a multitude of factors such as the assessment tool implemented, degree of clinical cognitive impairment, and the contribution of other neurobiological dysfunction. Studies on strategic macrostructural white matter damage in milder symptoms of depression or anxiety are still limited and further investigations are warranted to dissect the specific contributions of vascular brain injury on affective syndromes.

Strengths of this study include the large and geographical diverse sample which increases the generalizability of our results. The study cohorts also had similar neuropsychiatric scales, which benefited harmonization of data and interpretation of results. The analytic approach of examining of both class-based and ROI-based white matter tracts aids evaluation of tract-specific effects that reflect the systematic organization of white matter neuroanatomy. However, this study also has several limitations. Firstly, merging data from multiple cohorts that have different inclusion criteria, assessment protocols, and scanners may have resulted in heterogeneity in the pooled data. To minimize the heterogeneity, we have statistically adjusted for study site as a random effect and used previously established imaging processing pipelines to create uniform WMH maps in standardized space, allowing us to pool imaging data generated with different scanners and sequences. Secondly, the overall burden of NPS may have been underestimated as only the severity scores were harmonizable due to the different versions of NPI used. Although the neuropsychiatric syndromes used in this study have been replicated in large cohorts, possible misclassification of symptoms may have affected the results. Thirdly, future investigations may consider controlling for the potential effects of other

SVD (e.g. lacunes, microinfarcts), comorbidities, sociodemographic variables or neuropsychiatric medications that were not accounted for in this study. Future longitudinal studies investigating the impact of changes in strategic WMH with neuropsychiatric progression will be needed to elucidate possible causal relationships.

In conclusion, the tract-syndrome associations uncovered in this study provide insights into potential neurobiological projections that may be implicated in the manifestation of apathy and hyperactivity syndromes. Higher tract-defined WMH burden disrupting strategic cortico-cortical or cortico-subcortical networks may be a key mechanism through which SVD affects emotion and behavioral regulation in memory clinic patients.

LIST OF TABLES AND FIGURES

Table 1. Characteristics of the combined cohort.

Table 2. Associations of class-based white matter hyperintensities with neuropsychiatric syndrome severity.

Table 3. Associations of ROI-based white matter hyperintensities with neuropsychiatric syndrome severity.

Table S1. Characteristics of participant by cohorts.

Table S2. Frequencies of neuropsychiatric syndromes and individual symptoms by diagnosis.

Figure 1. White matter tracts of interest in each major class of white matter fiber bundles. The white matter tracts were generated using the John Hopkins University-atlas with a 10% probability threshold.

Figure 2. Overview of the prevalence of individual neuropsychiatric symptoms in each syndromes (% of cohort). Individual symptoms were classified under affective, apathy, hyperactivity, and psychosis syndromes following previous findings from the European Alzheimer's Disease Consortium.

Figure S1. Participant flowchart by cohort.

Contributors

CNK, MC, GJB, CPLHC, JMB, CHT conceptualised and designed the study. All authors contributed substantially to data acquisition and/or processing of their respective cohorts. CNK conducted the statistical analysis. CNK and CHT wrote the first draft. All authors provided important intellectual input to the draft and approved the final version of the manuscript. CHT and JMB contributed equally. CHT is the guarantor of the study.

DISCLOSURE

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TABLES

Table 1. Characteristics of the combined cohort.

	Total N = 2935
Age (years), mean (SD)	72.2 (8.4)
Sex, n (%)	
Male	1457 (49.6)
Female	1478 (50.4)
Education (years), mean (SD)	13.0 (4.5)
Diagnosis, n (%)	
Subjective cognitive impairment	581 (19.8)
Mild cognitive impairment	1167 (39.8)
Dementia	1187 (40.4)
MMSE, mean (SD)	24.9 (4.7)
CDR sum-of-boxes, median (IQR)	0.5 (0.5)
Neuropsychiatric syndrome, n (%)	
Affective	1178 (40.1)
Apathy	1119 (38.1)
Hyperactivity	1372 (46.7)
Psychosis	858 (29.2)
WMH volume (mL), median (IQR)	
Total WMH volume	6.2 (15.1)
Association WMH	0.98 (3.00)
Commissural WMH	1.10 (1.87)
Projection WMH	0.96 (2.04)
Brain parenchymal fraction, mean (SD)	0.70 (0.05)[#]

CDR = clinical dementia rating, MMSE = mini-mental state examination, WMH = white matter hyperintensities.
[#]missing in 344 (13.1%) cases.

Table 2. Associations of class-based white matter hyperintensities volume with neuropsychiatric syndrome severity scores.

	Affective			Apathy			Hyperactivity			Psychosis		
WMH (volume)	**B**	**SE**	***p***	**B**	**SE**	***p***	**B**	**SE**	***p***	**B**	**SE**	***p***
Association fibers	-0.02	0.08	0.801	0.11	0.07	0.116	**0.31**	**0.12**	**0.009***	-0.03	0.06	0.701
Commissural fibers	0.07	0.11	0.539	0.10	0.10	0.340	**0.47**	**0.17**	**0.006***	0.05	0.09	0.607
Projection fibers	-0.05	0.10	0.582	**0.24**	**0.10**	**0.013***	**0.39**	**0.16**	**0.016***	0.03	0.09	0.759

Adjusted for age, sex, diagnosis, study site. Bold indicates significance after FDR correction for multiple comparisons ($q < 0.05$).
*remained significant after further adjustment for brain parenchymal fraction (missing 13.1% of cases) (data not shown).
WMH = white matter hyperintensities.

Table 3. Associations of ROI-based white matter hyperintensities volume with neuropsychiatric syndrome severity scores.

	Affective			Apathy			Hyperactivity			Psychosis		
WMH (volume)	**B**	**SE**	***p***	**B**	**SE**	***p***	**B**	**SE**	***p***	**B**	**SE**	***p***
Cingulum cingulate gyrus	-1.24	0.54	0.021	0.15	0.51	0.766	0.98	0.86	0.256	-0.17	0.47	0.723
Cingulum hippocampus	-10.8	8.84	0.222	-1.5	8.43	0.859	-1.42	14.2	0.920	2.19	7.76	0.777
Inferior fronto-occipital fasciculus	-0.01	0.11	0.987	0.25	0.11	0.024	**0.50**	**0.18**	**0.006***	0.02	0.10	0.811
Inferior longitudinal fasciculus	-0.11	0.19	0.572	0.15	0.18	0.422	0.52	0.31	0.089	0.01	0.17	0.942
Superior longitudinal fasciculus	-0.04	0.09	0.681	0.13	0.08	0.108	0.28	0.14	0.042	-0.08	0.08	0.312
Superior longitudinal fasciculus (temporal)	-0.50	0.77	0.517	1.15	0.73	0.115	2.72	1.23	0.027	0.46	0.67	0.496
Uncinate fasciculus	0.28	0.65	0.669	**1.82**	**0.67**	**0.005***	2.41	1.03	0.020	-0.10	0.56	0.866
Forceps major	0.10	0.12	0.379	0.02	0.11	0.890	**0.48**	**0.18**	**0.009***	0.03	0.10	0.733
Forceps minor	-0.08	0.20	0.683	**0.61**	**0.19**	**0.001***	0.54	0.32	0.090	0.15	0.17	0.384
Anterior thalamic radiation	-0.07	0.12	0.590	0.28	0.12	0.015	**0.49**	**0.19**	**0.011***	0.03	0.11	0.775
Corticospinal tract	-0.06	0.13	0.657	0.29	0.13	0.022	0.35	0.22	0.101	0.05	0.12	0.688

Adjusted for age, sex, diagnosis, study site. Bold indicates significance after FDR correction for multiple comparisons ($q < 0.05$).
*remains significant after further adjustment for brain parenchymal fraction (missing 13.1% of cases) (data not shown).
ROI = region of interest, WMH = white matter hyperintensities.