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Subcortical Unilateral Spatial Neglect is caused by White Matter Tracts in Subacute Stroke.

Tshetiz Dahal (MBBS), Narendra Singh, Anil Tamang (MBBS)
General Physician, Clinical Researcher and Writer, Affiliation : Lugansk State Medical University, Luhansk Oblast, 93000 Luhansk, Ukraine
Amity Institute of Biotechnology & Nanotechnology, Rajarhat, New Town, Kolkata
Medical Officer, Ganeshman Singh Memorial Hospital and Research Center, Mahalaxmisthan-15, Lalitpur, Nepal 44600, Frontline Hospital, Old Baneshwor, Kathmandu, Nepal 44600

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ABSTRACT
Context: Unilateral spatial neglect (USN) is prevalent after a stroke and is related with poor motor and cognitive results as well as a lower quality of life. Traditionally, cortical areas such as the posterior parietal cortex were assumed to be the neurological foundations of USN. Patients with stroke involving only subcortical structures, on the other hand, may also manifest with USN. While there have been few research on USN in subcortical stroke, one plausible reason for subcortical neglect is the involvement of white matter pathways connected to brain networks of visuospatial attention. As a result, the purpose of this study was to determine which specific white matter pathways constitute neurological substrates for USN in patients with subcortical stroke.
Methods: Twenty-two patients admitted to the Department of Rehabilitation Medicine at Lugansk State Medical University and Hospital,Ukraine with subcortical stroke but no cortical damage were included retrospectively. Nine patients were classed as "USN(+)" since they scored 1 or higher on the Catherine Bergego scale and had at least two positive outcomes on three tests (the Schenkenberg line bisection test, Albert's test, and home drawing test). The remaining 13 participants with no anomalies on those tests were classed as "USN(-)." MRI stroke lesions were manually drawn using the MRIcron software. MRI scans were subjected to lesion overlapping and atlas-based analysis. The Albert test and the Catherine Bergego scale was used to examine the relationship between the overlapping lesion volumes with white matter regions and the severity of USN.
Results: Lesions were more common in the USN(+) group than in the USN(-) group, despite having similar locations in the right hemisphere. The atlas-based studies revealed that the lesions in the USN(+) group overlapped substantially more with the right cingulum in the cingulate cortex, the temporal projection of the superior longitudinal fasciculus, and the forceps minor than the lesions in the USN(-) group. The volume of the implicated white matter tracts corresponded with the Catherine Bergego scale score.
Conclusion: White matter pathways related with USN were discovered in patients with subcortical stroke without cortical involvement in this investigation. Our findings, coupled with earlier research on subcortical USN, support the theory that USN is caused by disruption to white matter networks.
Keywords: Stroke, Subcortical, Unilateral Spatial Neglect, Atlas-based lesion overlapping analysis, White matter tract

I. INTRODUCTION

Following a stroke, the prevalence of unilateral spatial neglect (USN) is roughly 30%. (1). Although patients are expected to recover from USN with time, it can last for more than a year (2, 3). In stroke patients, the presence of USN is associated with poor motor and cognitive results as well as a lower quality of life (4, 5). Furthermore, the severity of USN is associated with functional outcomes following a right hemisphere stroke (6). Furthermore, USN raises the danger of falls and the strain on carers (7, 8). Based on an early observational research, functional brain regions connected to USN were considered to be cortical areas like as the posterior parietal cortex (9). Anatomo-clinical correlation studies using structural brain imaging, on the other hand, have revealed that the inferior parietal lobule is closely related with USN symptoms (10). Furthermore, injury to the right superior temporal gyrus or the ventrolateral prefrontal brain has been linked to USN in other investigations (11–13).

However, USN has been recorded in patients with subcortical stroke who did not have cortical areas involved (3). Aside from the potential role of subcortical grey matter deficits in USN (14), a few prior investigations have indicated that white

matter tracts implicated in visuospatial networks can also cause USN. The superior longitudinal fasciculus, inferior occipitofrontal fasciculus, and superior occipitofrontal fasciculus were linked with USN in a study of 140 patients with acute cortical and subcortical strokes (15). On diffusion tensor imaging, another research of 45 chronic cortical and subcortical stroke patients revealed decreased fractional anisotropy in the right superior longitudinal fasciculus (SLF) and the splenium of the corpus callosum (16).A recent research of 174 patients with acute cortical and subcortical strokes found that tracts from the right parietal cortex and left or right mesial temporal cortex were highly related with USN (17). Furthermore, Umarova et al. found that patients with USN following a stroke of the right middle cerebral artery territory had a symptom-correlating drop in fractional anisotropy in regions associated to the left dorsal attention system (18). According to Bartolomeo et al., white matter networks connecting frontal and parietal areas may have an important role in the pathophysiology of USN (19). However, the aforementioned investigations included individuals with both cortical and subcortical stroke (15-18), implying that the involvement of white matter tracts may change depending on whether the lesion is cortical or subcortical. Because subcortical stroke can cause aberrant connection throughout or across hemispheres (20), examining neurological mechanisms connected to USN with a focus on subcortical stroke is worthwhile. Furthermore, because recovery through reconfiguration of the structure-function link may complicate the lesion-symptom analysis (17), examining stroke patients in the early stages might give valuable insights. As a result, the purpose of this study was to look at specific white matter tracts as neurological substrates for USN in patients with subcortical stroke who had no cortical involvement, utilizing atlas-based white matter involvement and voxel-based lesion overlapping analyses.

II. MATERIALS AND METHODS

From January 2017 to June 2021, we reviewed the data of patients admitted to the Department of Rehabilitation Medicine at Poltava Regional Clinical Hospital . We identified individuals who had their first right hemisphere stroke and only involved subcortical brain areas such as the basal ganglia, thalamus, internal capsule, and corona radiata. We included patients whose records included an initial brain magnetic resonance imaging (MRI) assessment as well as an examination for unilateral spatial neglect (USN) consisting of the Schenkenberg line bisection test (21), Albert's test (22), and the home drawing test among those included. Patients with no anomalies in the three tests were classified as "USN(-)" (n = 13). Those with abnormalities in at least two of three tests (omission of two or more whole lines on the left side in the line bisection test; omission of over 70% of lines uncrossed on the left side of the midline in the Albert test (22); and omission of any significant omissions on the left side (such as door, window, roof, chimney, and smoke) in the house drawing test) were further evaluated with the Catherine Bergego scale (23) to find clinically meaningful USN. Those having a Catherine Bergego scale score of 1 or higher (24) were then classified as part of the "USN(+) group" (n = 9). The evaluation was carried out and recorded by trained occupational therapists. Supplementary Table 1 shows the results of the USN evaluation.

MRI Data Acquisition and Preprocessing

T1-weighted magnetic resonance (MR) images were collected at Poltava Regional Clinical Hospital using a 3.0 T MRI (Siemens Trio Trim scanner) and a magnetization-prepared fast gradient echo sequence (TE/TR/T1=2.32 ms/2.3 s/900 ms; 256 256 192 matrix for 1 mm3 isovoxels). Images of fluid-attenuated inversion recovery (FLAIR) were also taken to help locate lesions. When FLAIR images were unavailable, diffusion-weighted imaging (DWI) findings were employed in four cases [all in the USN(-) group]. To conduct our retrospective analysis, we mapped all of the participants' lesions into the same standard space. First, each subject's FLAIR picture was linearly co-registered with their T1-weighted image. The T1-weighted picture was then normalized to the standardised International Consortium for Brain Mapping (ICBM) template for East Asian brains supplied by Statistical Parametric Mapping (SPM). Following that, the co-registered FLAIR pictures were registered and resliced on the ICBM template using the parameters gained in the preceding steps. This two-step procedure could result in more accurate image normalization. Finally, using MRIcron software, the neuroanatomy specialists (SK and SHL) manually delineated lesions onto the aligned images (25). These ROI photos from the standardised template were used in the analysis.This methodology has been described in detail in a previous study (26). All preprocessing was performed using SPM12 software (27–29).

Clinical Evaluation of White Matter Tract involvement

We looked at how the lesions affected each patient's white matter tracts. We used the

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volumetric white matter tracts established in Johns Hopkins University's white matter atlas (30, 31). It has 20 tracts in total, but we only included 11: the anterior thalamic radiation, cingulum in the cingulate cortex, cingulum in the hippocampal area, corticospinal tract, forceps major, forceps minor, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, superior longitudinal fasciculus, temporal projection of the SLF, and uncinate fasciculus connected to the right hemisphere The overlapping volume of each individual's lesions was then measured. We used permutation testing (32, 33) to compare the overlapped volumes between groups because the number of subjects was small and the distribution of overlapped volumes was not normally distributed (Supplementary Figure 3); specifically, permutation-based ANCOVA (34) was used and adjusted for age and gender, with a permutation number of 1,000. As a multiple comparison correction, we utilised a false discovery rate (FDR) technique on the 11 white matter tracts (35). Furthermore, in the USN(+) group, we conducted a correlation research between the overlapped volume of white matter tracts and USN severity scores: the percentage of total uncrossed lines in the Albert test and the Catherine Bergego scale score. The severity scores were skewed, and the sample size was small; therefore, we used the Spearman correlation coefficients. For the statistical analyses, our in-house codes and the LinStat library (2006b) (36) in a MATLAB (2019a, MathWorks) were used.

Evaluation of Lesion Recurrence

We also examined at how group-level lesions intersected with the 11 white matter tracts. This is an additional graphic to the previous statistical analysis. This shows an overall involvement of white matter tracts but differs from the statistical analysis results. We began by obtaining group-level lesions from all patients in the USN(+) and USN(-) groups. The latter was subsequently removed from the former to extract symptom-related lesions. These symptom-related lesions were then layered on top of the 11 white matter tracts in the FMRIB software library v5.0.9 (37) and displayed with BrainNet Viewer (38) and voxel lesion symptom mapping (VLSM, version 2.55; https://aphasialab.org/vlsm/). Regarding the latter, please keep in mind that we did not perform VLSM but rather used it to structure our visualisation in Figure 1 and Supplementary Figures 1, 2.

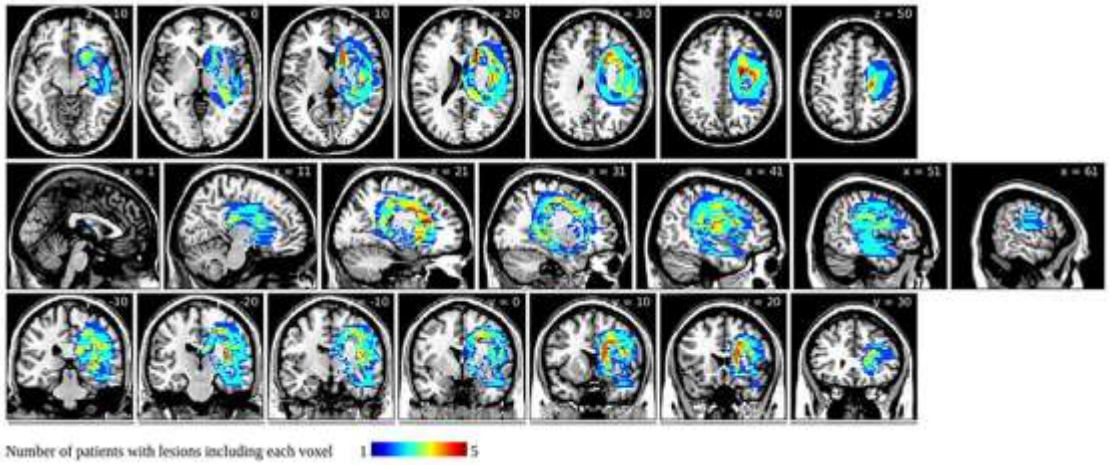

Figure 1. Symptom-related lesions obtained by subtracting group-level unilateral spatial neglect (USN)(–) lesions from group-level USN(+) lesions. Warmer colors indicate larger numbers of subjects with overlapping lesions in the USN(+) group.

III. RESULTS

Characteristics of the Subject

Table 1 compares the features of the USN(+) group to those of the USN(-) group. The mean age of the USN(+) patients was substantially lower than that of the USN(-) patients (54.4 vs. 69.2 years). Furthermore, the median lesion volume in the USN(+) group was substantially greater (68,328 vs. 21,416 mm3). There were no significant differences between the two groups in terms of sex, stroke type and site, days from onset to imaging, or days from onset to evaluation.

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	Unilateral spatial neglect ($n = 9$)	No unilateral spatial neglect ($n = 13$)	*Test statistics*	*p*-value
Age, years	54.4 ± 16.3	69.2 ± 12.2	−2.437[a]	0.024*
Male, n (%)	6 (66.7%)	10 (76.9%)	0.282[b]	0.595
Stroke type, n (%)			3.010[b]	0.083
Ischemic	1 (11.1%)	6 (46.2%)		
Hemorrhagic	8 (88.9%)	7 (57.1%)		
Stroke location, n (%)			2.996[b]	0.558
Basal ganglia	6 (66.7%)	5 (38.5%)		
Thalamus	2 (22.2%)	3 (23.1%)		
Internal capsule	1 (11.1%)	2 (15.4%)		
Basal ganglia & internal capsule	0 (0%)	2 (15.4%)		
Corona radiata	0 (0%)	1 (7.7%)		
Lesion volume, median (IQR)	68328 (176060)	21416 (22044)	6.095[c]	0.024*
Onset to imaging, days, median (IQR)	0 (1.5)	1 (1)	51.0[d]	0.647
Onset to evaluation, days, median (IQR)	14 (10)	14 (7.5)	76.5[d]	0.235

*Statistically significant results. IQR, interquartile range.
[a]t-statistics of 2-sample t-test, [b]χ^2 value of Chi-Square test, [c]F-statistics of ANCOVA controlling for the effects of age and sex, [d]U statistics of Mann-Whitney U test.

Table 1. Comparing the baseline characteristics. Clinical characteristics for each patient are shown in Supplementary Table 1.

Lesion Recurrence Results

Supplementary Figures 1 and 2 show group-level lesions in the USN(+) and USN(-) groups, respectively. Both groups' overlapping lesions were situated in the right hemisphere; however, the lesions in the USN(+) group were more extensive than those in the USN(-) group. Figure 1 depicts group-level lesions of the USN(-) group subtracted from those of the USN(+) group. They affected the caudate nucleus, the internal capsule, and the corpus callosum, but not the thalamus, putamen, globus pallidus, or corona radiata.

Involvement of white matter tracts

The involvement of the right anterior thalamic radiation, corticospinal tract, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, uncinate fasciculus, superior longitudinal fasciculus and its temporal projection, cingulum in the cingulate cortex, and the slight involvement of the cingulum in the hippocampal area, forceps major, and forceps minor was revealed by the overlap with the white matter tracts (Figure 2). These diagrams, however, provide a crude representation of the overlapping lesion areas and hence cannot depict the statistical difference between the groups.

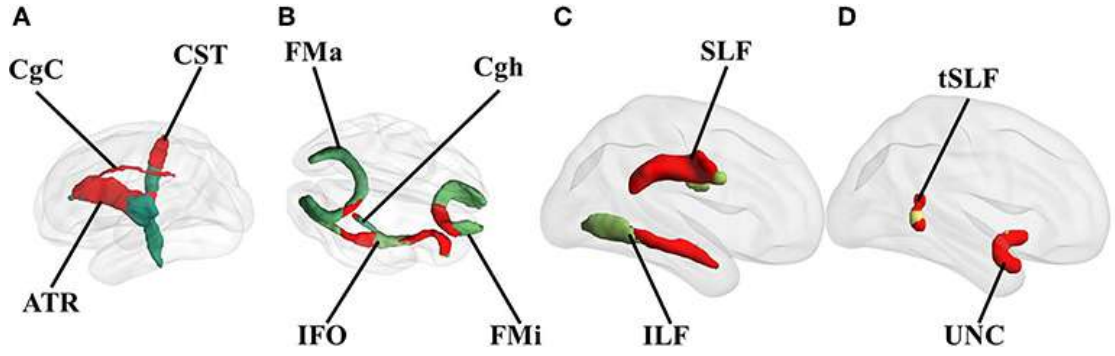

Figure 2. Overlap of white matter tracts with the identified symptom-related lesions. Red represents the overlapping parts of the white matter tracts with the lesions. Only the involved tracts are shown. All overlapping tracts located in the right hemisphere. (A) medial view, (B) transverse view, and (C,D) lateral view of the right hemisphere. CST, corticospinal tract; ATR, anterior thalamic radiation; CgC, cingulum in the cingulate cortex; CgH, cingulum in the hippocampal area; FMa, forceps major; FMi, forceps minor; IFO, inferior fronto-occipital fasciculus; SLF, superior

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longitudinal fasciculus; ILF, inferior longitudinal fasciculus; UNC, uncinate fasciculus.

When we compared white matter tract involvement using the overlapped volumes between the individual's lesions and volumetric white matter tracts while controlling the effects of age and sex using permutation-based ANCOVA, we observed widespread overlaps on the tracts in the USN(+) group (Table 2). The statistical analysis ruled out white matter tracts that were involved to similar degrees in both groups. We observed that the right cingulum in the cingulate cortex [F (1, 20) = 5.074, FDR-adjusted p = 0.026; all p-values in this and the following section are FDR-adjusted], the temporal projection of the superior longitudinal fasciculus (F = 6.724, p = 0.026), and the forceps minor (F = 3.468, p = 0.026) were significantly affected. In other words, the volume of the involved white matter tracts was greater in the USN(+) group than in the USN(–) group after adjusting for age and sex. The anterior thalamic radiation (p = 0.077), superior longitudinal fasciculus (p = 0.081), and forceps major (p = 0.077) were marginally affected. Detailed results regarding the differences between both groups are listed in Supplementary Figure 3 as a histogram.

Relationship between USN Severity and White Matter Tract involvement

The cingulum in the cingulate cortex, the forceps minor, the temporal projection of the superior longitudinal fasciculus, and the severity of the USN were the white matter tracts significantly impacted in the USN(+) group (the percentage of total uncrossed lines in the Albert test and the Catherine Bergego scale score). We specifically discussed the relationship between two USN severity parameters and the overlapping volume of the damaged white matter tracts (Supplementary Table 2). The percentage of all uncrossed lines did not significantly correspond with the involvement of the white matter tracts. However, the score of the Catherine Bergego scale was significantly correlated with the white matter tracts involvement (r = 0.822, p = 0.012 for the cingulum in the cingulate cortex; r = 0.897, p = 0.002 for the forceps minor; r = 0.895, p = 0.003 for the temporal projection of the superior longitudinal fasciculus). The scatter plots are illustrated in Supplementary Figure 4.

White matter tractography atlas	Unilateral spatial neglect ($n = 9$) median [25...75%]		No unilateral spatial neglect ($n = 13$) median [25...75%]		*F*-statistics	uncorrected *p*-value	FDR-adjusted *p*-value
Anterior thalamic radiation R	2720	[182...4868]	480	[0...1722]	4.815	0.035	0.077
Corticospinal tract R	1664	[1352...2904]	1216	[496...1588]	2.795	0.115	0.141
Cingulum (cingulate gyrus) R	0	[0...164]	0	[0...0]	5.074	0.006	**0.026***
Cingulum (hippocampus) R	0	[0...14]	0	[0...0]	2.858	0.101	0.139
Forceps major	0	[0...184]	0	[0...0]	4.255	0.028	0.077
Forceps minor	16	[0...442]	0	[0...0]	3.468	0.007	**0.026***
Inferior fronto-occipital fasciculus R	1976	[284...3872]	72	[0...2182]	2.482	0.143	0.157
Inferior longitudinal fasciculus R	16	[0...1638]	0	[0...42]	3.511	0.083	0.130
Superior longitudinal fasciculus R	4000	[1004...7256]	88	[0...658]	4.859	0.044	0.081
Uncinate fasciculus R	176	[0...442]	0	[0...190]	1.792	0.184	0.184
Superior longitudinal fasciculus (temporal projection) R	0	[0...26]	0	[0...0]	6.724	0.004	**0.026***

p-values were calculated through permutation-based ANCOVA controlling for the effects of age and sex.
*Statistically significant results after the FDR procedure.

Table 2. Overlap (mm3) of the lesions in each group with the major White Matter Tracts.

IV. DISCUSSION

Using atlas-based lesion overlapping analysis, this study examined white matter tract involvement as a structural neurological basis of USN in subcortical stroke. Only individuals with subcortical strokes and no cortical abnormalities were included in the research population. As a result, the findings of this study do not account for cortical participation in USN. In comparison to the USN(-) group, the USN(+) group exhibited more widely dispersed lesions and larger lesion volumes. The right cingulum in the cingulate cortex, the temporal projection of the superior longitudinal fasciculus, and the forceps minor were the specific white matter pathways impacted by USN. The Catherine Bergego scale score and the involvement of white matter tracts were linked with the severity of the USN, however the Albert test's total number of uncrossed lines was not. This supports that USN may result from the disconnection of white matter tracts (19). The medial temporal regions and sub-genual frontal area are connected by longer fibres in the cingulum, which is a portion of the limbic system. Adjacent medial parietal and frontal lobes

are connected by shorter fibres (39). The dorsal cingulum is linked to executive skills including attention and planning, whereas the temporal cingulum is linked to learning and episodic memory (40). According to a study on healthy volunteers, the cingulum may help to coordinate spatial attention (41). Few research have looked into the relationship between the cingulum (as white matter tracts) and USN, despite the cingulate cortex having been linked to USN symptoms after stroke (42).

According to a research evaluating patients with motor neglect, injury to the cingulum is linked to motor neglect, presumably through causing unilateral medial motor system malfunction (43). The cingulum in the cingulate cortex is strongly correlated with USN in subacute subcortical stroke, according to our most recent findings, which are consistent with earlier research. Our study only evaluated visuospatial neglect, thus more research into different forms of USN is necessary. The frontal cortex and the temporal, parietal, and occipital lobes are connected by the superior longitudinal fasciculus, which is important for language, focus, memory, and emotions (44). Prior research has shown that patients with USN after stroke are consistently found to have damage to the superior longitudinal fasciculus (15, 16, 45). Additionally, various sites of the implicated superior longitudinal fasciculus were hypothesized to play a part in various USN characteristics (46). However, the temporal projection of the superior longitudinal fasciculus was more specifically impacted, and future studies on the correlation between lesions or locations of white matter tracts using more sensitive imaging modalities like diffusion tensor imaging could support this. Similarly, our current results show that the superior longitudinal fasciculus is closely associated with USN.

The biggest nerve fibre that unites the two brain hemispheres is called the corpus callosum (47). The splenium of the corpus callosum connecting the occipital lobes supplies fibres to the forceps major, whereas the genu of the corpus callosum connecting the frontal lobe areas supplies fibres to the forceps minor (48). Prior research on USN discovered decreased fractional anisotropy in the forceps major and splenium of the corpus callosum, facilitating interhemispheric communication (16, 49). A recent study found that increasing the functional connection between the right posterior parietal cortex and the left superior temporal gyrus while at rest caused USN symptoms in the right posterior parietal brain (50).

This impact also showed fractional anisotropy in the posterior corpus callosum, suggesting that callosal anisotropy may be able to predict changes in the attentional network. Our recent findings demonstrate a substantial relationship between the forceps minor and USN, which is consistent with these research.

Age-related increases in risk and USN severity are seen in stroke patients (51, 52). Possible causes included brain atrophy, white matter disorders, or a history of ischemia events, which are frequent in elderly people. Sex was not related to the frequency, intensity, or types of USN, though (52, 53). Additionally, there was no discernible variation in visuospatial perception between haemorrhage patients and infarction patients with similar demographics (54). When the lesion volume of the affected white matter tracts was examined in our study after adjusting for age and sex, it became clear that the USN(+) group had more involvement than the USN(-) group did. Future studies involving additional ischemic stroke patients with USN will further examine the impact of stroke type on USN because just one patient in the USN(+) group experienced an infarction.

According to earlier research, cortical hypoperfusion may be closely related to USN in subcortical stroke. Hillis et al. revealed that contemporaneous cortical hypoperfusion was highly linked with USN rather than the lesion site in 14 participants with solely subcortical lesions; however, a lesion comparison analysis between cases and controls was not carried out (55). Another study employing perfusion imaging in 50 patients with acute right subcortical infarcts discovered that USN was substantially correlated with hypoperfusion of the right superior temporal gyrus or right angular gyrus rather than the subcortical infarct itself (56). However, as this study did not use a voxel-based analysis but rather Brodmann area landmarks, specific atlas-based white matter pathways could not be identified. Therefore, it would be helpful to do further research utilizing voxel-based lesion analysis together with supplementary perfusion imaging to pinpoint the precise connection between lesions affecting subcortical white matter tracts and cortical hypoperfusion in the development of USN. Our study has a number of drawbacks. First, despite the fact that there may not have been enough individuals included, the mean age of the patients in the USN(+) group was considerably lower than that of the USN(-) patients. A permutation-based ANCOVA was used to adjust the results for age and sex. Second, the standard voxel-based lesion symptom mapping (VLSM)

could not be used due to inadequate statistical power due to the insufficient number of participants. We substituted a straightforward lesion overlapping analysis. Third, our approach to analyzing white matter tract involvement may have been overly simplistic. We were unable to do a detailed investigation of white matter degeneration because we lacked diffusion tensor pictures. The JHU White Matter Atlas was utilised as an alternative.

However, the lesion that wasn't fully severed could have just warped the real white matter tracts. In certain circumstances, the analysis can produce false results. The overlapped lesion and white matter tract volumes were also measured. Even when the JHU atlas has caught the white matter architecture of the patients, a higher volume overlap may not always mean that the tracts are unconnected. The tracts may be fully detached even with a very tiny overlap; yet, even with a huge overlap volume, the narrow cross-section of the tracts may have been kept, saving the tracts. Such alternatives were not taken into account in our investigation, therefore our results should be evaluated with some care. Finally, only egocentric and peripersonal USN categories were considered in our evaluation of USN. Other USN categories, like allocentric, intra-personal, and motor USN, were therefore not examined. Additionally, since occupational therapists rather than the patients evaluated the Catherine Bergego scale score, the anosognosia could not be assessed. Future investigations into the role of the white matter tract utilizing more advanced and varied evaluation techniques would be beneficial.

V. CONCLUSION

The right cingulum in the cingulate cortex, the temporal projection of the superior longitudinal fasciculus, and the forceps minor, among other white matter tracts, are strongly associated with USN in patients with subacute subcortical stroke without cortical involvement, according to atlas-based lesion overlapping analyses. By ruling out the potential impacts of cortical involvement, we also supported the earlier theory that USN may be caused by damage to white matter pathways rather than damage to a specific cortical region (19). The findings of the current study may be extended by our special study population to those of earlier research on subcortical USN and provide convincing proof of white matter involvement.

ETHICS STATEMENT

This study was approved by the Lugansk State Medical University Institutional Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the clinical research requirements.

CONFLICT OF INTERESTS

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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