A voxel- and source-based morphometry analysis of grey matter volume differences in very-late-onset schizophrenia-like psychosis

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Abstract

Background. Very-late-onset schizophrenia-like psychosis (VLOSLP) is associated with significant burden. Its clinical importance is increasing as the global population of older adults rises, yet owing to limited research in this population, the neurobiological underpinnings of VLOSP remain insufficiently clarified. Here we address this knowledge gap using novel morphometry techniques to investigate grey matter volume (GMV) differences between VLOSLP and healthy older adults, and their correlations with neuropsychological scores.
Methods. In this cross-sectional study, we investigated whole-brain GMV differences between 35 individuals with VLOSLP (mean age 76.7, 26 female) and 36 healthy controls (mean age 75.7, 27 female) using whole-brain voxel-based morphometry (VBM) and supplementary source-based morphometry (SBM) on high resolution 3D T1-weighted MRI images. Additionally, we investigated relationships between GMV differences and cognitive function assessed with an extensive neuropsychological battery.
Results. VBM showed lower GMV in the thalamus, left inferior frontal gyrus and left insula in patients with VLOSLP compared to healthy controls. SBM revealed lower thalamo-temporal GMV in patients with VLOSLP. Processing speed, selective attention, mental flexibility, working memory, verbal memory, semantic fluency and confrontation naming were impaired in patients with VLOSLP. Correlations between thalamic volumes and memory function were significant within the group of individuals with VLOSLP, whereas no significant associations remained in the healthy controls.
Conclusions. Lower GMV in the thalamus and fronto-temporal regions may be part of the underlying neurobiology of VLOSLP, with lower thalamic GMV contributing to memory impairment in the disorder.

Introduction

Although schizophrenia generally surfaces in adolescence, several studies report on individuals who first experienced psychosis very late in life, in the absence of a mood disorder or a neurological illness (Sharma, Debsikdar, Naphade, & Shetty, 2014). Individuals with an onset of psychotic symptoms after 60 years are referred to as very-late-onset schizophrenia-like psychosis (VLOSLP) according to an international expert consensus (Howard, Rabins, Seeman, Jeste, & The International Late-Onset Schizophrenia Group, 2000). Compared with early-onset schizophrenia (EOS), VLOSLP is mainly characterised by positive psychotic symptoms, whereas affective blunting and disorganisation are usually absent. The community prevalence of VLOSLP is only 0.1% to 0.5% (Copeland et al., 1998). However, there is a linear trend in the relationship between age and onset of non-organic and non-affective psychosis after the age of 60, exhibiting an 11% increase in VLOSLP with each 5 year increase in age (van Os, Howard, Takei, & Murray, 1995). As the older age groups are the fastest growing section of the world population, healthcare may thus be increasingly confronted with a first onset of psychosis in elderly patients. Further elucidation of the neurobiological mechanisms of VLOSLP, also leading to debilitating symptoms such as cognitive and functional impairment, is urgently needed.

There is only limited research on neurobiological changes specifically in individuals with VLOSLP. Most research was conducted in samples of individuals with late onset schizophrenia (>40 years; LOS) or a mixed group of individuals with LOS and VLOSLP (Van Assche, Morrens, Luyten, Van de Ven, & Vandenbulcke, 2017). These studies have reported an increased ventricle-to-brain ratio and larger third ventricles (Corey-Bloom, Jernigan,

Archibald, Harris, & Jeste, 1995; Lesser et al., 1993; Rabins, Pearlson, Jayaram, Steele, & Tune, 1987), decreased volumes in the amygdala, entorhinal cortex, hippocampus and anterior superior temporal gyrus (Barta et al., 1997; Casanova, 2010; Sachdev, Brodaty, Cheang, & Cathcart, 2000), subcortical volume as well as temporal lobe volume reductions (Howard, Förstl, Almeida, Burns, & Levy, 1992a; Howard, Förstl, Naguib, Burns, & Levy, 1992b; Rabins, Aylward, Holroyd, & Pearlson, 2000), greater thalamic volumes (Corey-Bloom et al., 1995), and cerebellar atrophy (Barak, Aizenberg, Mirecki, Mazeh, & Achiron, 2002).

Consistent with findings in EOS, a marked cognitive impairment is one of the central aspects of late onset psychosis. Patients with LOS or VLOSLP show deficits in processing speed, attention, executive function, language and memory (Van Assche et al., 2017). Several aspects of processing speed are affected, such as cognitive speed, psychomotor and complex visuo-perceptual speed (Henderson et al., 1998; Jeste et al., 1995; Naguib & Levy, 1987; Vahia et al., 2010). Attention, and specifically vigilance, appeared reduced in VLOSLP (Hanssen et al., 2015). In the domain of executive function, working memory is deficient, as well as fluency, cognitive flexibility, shifting, planning, abstraction and logical reasoning (Almeida et al., 1995a, 1995b; Girard et al., 2011; Östling, Johansson, & Skoog, 2004). Although the evidence for memory impairment in VLOSLP is not entirely consistent, many studies point to deficient encoding as well as consolidation skills (Almeida et al., 1995b; Brichant-Petitjean et al., 2013). There has been limited research into language function in LOS or VLOSLP, which points to a deficit in semantic processing (Heaton et al., 1994; Jeste et al., 1995). Impairments in the different neuropsychological domains in patients with LOS or VLOSLP are usually only mildly progressive in nature.

In the absence of a definitive understanding of the neurobiological underpinning of VLOSLP and those which lead to cognitive deficits, there are currently no biomarkers available to aid diagnosis and indicate the most suitable treatment. Neuroimaging studies have been conducted to identify differences between LOS/VLOSLP and normal ageing. However, previous studies have not focused solely on patients with VLOSLP, but rather a mixed group of LOS and VLOSLP. Additionally, most studies investigated pre-defined brain regions (Van Assche et al., 2017). To address the knowledge gap, we conducted a data-driven, voxel-based morphometry (VBM) analysis, which offers the advantage of an unbiased evaluation of the whole-brain in patients with VLOSLP to identify grey matter (GM) abnormalities for the first time. In addition to this mass univariate approach, a data-driven, multivariate extension of VBM, i.e. source-based morphometry (SBM), may provide complementary information on the neurobiology of psychiatric disorders as neuronal network disorders. This technique can identify spatially distinct regions which show similar patterns of GM abnormalities, and which may thus reflect alterations in a common structural network. Additionally, we aimed to detect neuropsychological deficits and link these to the volumetric differences in an attempt to clarify the neurobiological mechanisms of VLOSLP and its debilitating cognitive symptoms.

Methods

Participants

A group of 36 individuals with VLOSLP who were consecutively admitted to the old age psychiatry ward participated in the current study. Individuals with VLOSLP fulfilled the consensus criteria proposed by the International Late-Onset Schizophrenia Group with first onset of psychosis after the age of 60 and no evidence of neurologic or major affective disorder (Howard et al., 2000). Other somatic or ophthalmologic conditions that might explain the onset of psychosis in late life had also been excluded. Thirty-six healthy older adults were also recruited using flyers. Additional exclusion criteria for both groups were (comorbid) major psychiatric illness, and previous or current alcohol or drug dependence. The current study was approved by the Ethics Committee of the University Hospitals of Leuven and all participants signed an informed consent.

MRI acquisition and image processing

High-resolution T1-weighted images were acquired on a 3T Philips Achieva scanner with an 8-channel head coil. High-resolution 3D turbo field echo (3DTFE) T1-weighted images were acquired with parameters: TR = 9.6 ms, TE = 4.6 ms, flip angle = 8°, voxel-size = $0.98 \times 0.98 \times 1.2$ mm^3, 182 axial slices.

All T1-images were processed using the default pipeline of the Computational Anatomy Toolbox (CAT12.6, http://dbm.neuro.uni-jena.de/cat/), a toolbox for Statistical Parametric Mapping software (SPM12, version 7771, http://www.fil.ion.ucl.ac.uk/spm). Prior to preprocessing, all data were visually checked and manually aligned to the origin of images with the anterior commissure–posterior commissure line. Preprocessing included bias-correction, segmentation into GM, WM and CSF, spatial normalisation using the Diffeomorphic Anatomical Registration using Exponentiated Lie Algebra (DARTEL) algorithm, and modulation. Images were smoothed with an 8-mm full-width at half maximum Gaussian kernel (FWHM). Total intracranial volume (TIV) was calculated using CAT12.

Multivariate SBM analysis

SBM is a data-driven, multivariate extension of VBM utilising independent component analysis (ICA) to identify patterns across multiple covarying networks (Xu, Groth, Pearlson, Schretlen, & Calhoun, 2009). Using individual pre-processed GM image, we performed an ICA. An Infomax algorithm implemented in the SBM module of the GIFT toolbox (http://mialab.mrn.org/software/gift) was used to perform ICA decompositions. We set the number of components to 30 in accordance with similar studies (Gupta et al., 2015; Xu et al., 2009), and we used the ICASSO algorithm (Himberg, Hyvärinen, & Esposito, et al., 2004) to increase component reliability and consistency. Components with a quality index >0.9 indicating stable decomposition were used in subsequent analyses. Group comparisons were conducted by using ICA loading parameters. A multivariate analysis of covariance (MANCOVA) was used with loading parameters as dependent variables, diagnosis as a factor, and age as a covariate. We set $p < 0.05$ as a statistically significant threshold. The following separate ANCOVAs including age as a covariate were conducted to identify which components differed between groups. Detailed description of methodology for SBM can be found in the supplementary materials and a previous paper (Xu et al., 2009).

Neuropsychological assessments

The following instruments were administered by trained neuropsychologists in a standardised way according to published test

manuals. A standardised version of the Mini Mental Status Examination (MMSE) was used as a tool for the assessment of global cognitive abilities (Folstein, Folstein, & McHugh, 1975).

The Stroop test (Stroop, 1935) and Digit Span forward and backward tests (Jones & Macken, 2015; Miller, 1956) were used to assess processing speed, attention and executive function. Stroop I was used to assess processing speed and Stroop Interference Factor (IF) was used to estimate selective attention, mental flexibility and inhibitory control (Van der Elst, Van Boxtel, Van Breukelen, & Jolles, 2006). The Digit Span forward and backward are the most frequently used instruments to measure attention span, verbal storage and rehearsal systems. The maximum number of digits repeated in the same and in reverse order was used as estimates of attention/memory span and working memory respectively.

The Rey Auditory Verbal Learning Test (RAVLT) (Rey, 1964) and animal verbal fluency (AVF) (Benton, 1968) tasks were used to assess episodic and semantic memory respectively.

The Boston Naming Test was used to assess confrontation naming skills (Goodglass, Kaplan, & Weintraub, 1983; Rabin, Paolillo, & Barr, 2016) because it is a well-established reliability and validity among different healthy and clinical populations (Strauss, Sherman, & Spreen, 2006). The number of items accurately named without offering semantic or phonetic cues constitutes the total score.

Statistical analysis

Descriptive statistics were used to analyse the clinical data. Distributions of all variables were inspected using histograms, q–q plots, and Shapiro–Wilk tests. Whole-brain analyses were conducted using SPM12, and other analyses were conducted by using SPSS *v.* 25.

To investigate any differences in grey matter volume (GMV) between patients with VLOSLP and healthy controls, whole-brain voxel-wise comparisons were performed using SPM12, with age and TIV as covariates. The statistical threshold for the voxel-wise whole-brain analyses was set at family-wise error corrected $p < 0.05$ determined by threshold-free cluster enhancement (Smith & Nichols, 2009). An absolute threshold masking of 0.1 and a mask defined by AAL3 as an explicit mask were applied. Mango (http://ric.uthscsa.edu/mango/mango.html) and R version 3.4.3 were used to visualise the results.

To investigate significant differences between groups of participants on neuropsychological measures, we applied a MANCOVA (Pillai's trace because of the relatively small sample sizes) model with groups (with and without psychosis) as independent variable, test scores as dependent variables, and age as a covariate. Partial correlations were used to explore associations between regional GMV differences based on the results in the whole-brain analysis and neuropsychological measures. Age and TIV were included as covariates. For these analyses, we also set $p < 0.05$ as the statistically significant threshold following Bonferroni correction.

Results

Population and clinical characteristics

There were no significant group differences in age ($p = 0.47$) and gender ($p = 1.0$) (Table 1). Individuals with VLOSLP showed statistically significantly lower MMSE scores compared to healthy controls ($t(51) = 7.77$, $p < 0.001$). Psychotic symptoms consisted mainly of paranoid delusions (89%), often combined with (multimodal) hallucinations. When comparing the neuropsychological functioning of both participant groups with age as a covariate, there was a significant effect of group on neuropsychological results ($V = 0.53$, F (9, 60) = 7.40, $p < 0.001$). Separate t tests for each variable revealed significant mean differences in all neuropsychological variables except the Digit Span forward and RAVLT recognition after applying Bonferroni correction. There were medium to large effect sizes for all significant differences (Table 2).

Whole-brain GMV comparison

Data from one participant with VLOSLP was excluded from further analyses as visual inspection of the scan revealed an infarction. The whole-brain voxel-wise analysis identified significant lower GMV in the thalamus and left frontal regions, including the inferior frontal gyrus (IFG) and insula (Fig. 1). No brain regions were larger in patients with VLOSLP compared with healthy older adults. The additional VBM analysis with a more liberal but with a standard statistical threshold found a significant volume reduction in the right hippocampus, right inferior temporal gyrus, and right cerebellum in addition to the thalamus and left insula (online Supplementary Table S1 and Fig. S1).

In order to gain further insights into the GMV differences within the thalamus, we overlayed our results on the AAL3 brain atlas. We found that the lower GMV region was mainly located in the anteroventral/ventral anterior (AV/VA) nucleus, ventral lateral (VL)

Table 1. Demographic characteristics of both participant groups

	HC $N = 36$ M (s.d.) Range	VLOSLP $N = 35$ M (s.d.) Range	t (df)	p value
Age (years)	75.72 (5.76)	76.72 (7.48)	−0.73 (69)	0.47
	67–90	60–91		
MMSE	28.86 (1.29)	25.17 (2.50)	7.77 (50.57)	<0.001
	26–30	19–29		
			X^2 (df)	p value
Gender	25% male	26% male	0.005 (1)	1.0

Note: HC, healthy controls; VLOSLP, Very-late-onset schizophrenia-like psychosis; M, mean; s.d., standard deviation; MMSE, Mini Mental State Examination.

Table 2. Neuropsychological results of both participant groups

	HC N = 36 M (s.d.) Range	VLOSLP N = 35 M (s.d.) Range	t (df)	p value	Partial eta-squared	Cohen's d (CL effect size %)
DS forward	5.39 (0.93) 3–7	5.00 (0.94) 3–7	1.749 (69)	0.085	0.04	
DS backward	4.17 (1.11) 2–6	3.43 (0.78) 2–5	3.239 (69)	0.002*	0.13	0.78 (71%)
Stroop I	54.50 (10.46) 39–90	74.46 (17.71) 46–120	−5.761 (54.85)	<0.004*	0.33	1.40 (83%)
Stroop IF	62.90 (19.03) 31–95.17	128.35 (71.31) 33.5–364.5	−5.251 (38.69)	<0.001*	0.29	1.28 (81%)
RAVLT sum	47.78 (11.30) 24–70	32.71 (11.12) 14–62	5.660 (69)	<0.001*	0.32	1.36 (83%)
RAVLT delayed recall	9.89 (3.92) 1–15	6.11 (3.99) 0–15	4.017 (69)	<0.001*	0.19	0.97 (75%)
RAVLT recognition	13.61 (1.70) 7–15	12.17 (2.58) 4–15	2.768 (58.46)	0.008	0.10	
AVF	20.14 (5.46) 9–33	15.00 (6.71) 5–43	3.543 (69)	0.001*	0.15	0.85 (72%)
BNT	50.63 (7.09) 30–60	44.79 (9.26) 27–59	2.981 (63.70)	0.004*	0.12	0.72 (69%)

Note: HC, healthy controls; VLOSLP, Very-late-onset schizophrenia-like psychosis; M, mean; s.d., standard deviation; Stroop IF, Stroop Interference Factor; DS, Digit Span; RAVLT, Rey Auditory Verbal Learning Test; AVF, animal verbal fluency; BNT, Boston Naming Test. After applying Bonferroni correction differences between the two groups were considered significant at a $p < 0.005$ level; * = $p < 0.005$. ES = Effect size: Cohen's d was used to measure effect sizes of the group differences (Zakzanis, Kielar, Young, & Boulos, 2001); CL effect size, common language effect size, the % chance that in randomly selected pairs of individuals the participant from one group would score higher than the participant from the second group.

nucleus, and mediodorsal nucleus (MD) nucleus. To investigate which cortical regions could be affected by the lower thalamic GM region, we overlayed our results on the Oxford Thalamic Connectivity Atlas (Behrens et al., 2003). We found that the lower thalamic GMV region detected in the whole-brain analysis mainly connects the prefrontal and temporal regions (Fig. 2).

SBM analysis

SBM analysis identified eight stable components in our cohort (online Supplementary Fig. S2). There was a significant main effect of diagnosis on ICA loading parameters ($F_{8, 61} = 2.87$, $p = 0.009$). Separate univariate ANCOVAs revealed that there was a main effect of diagnosis in the component 2 (thalamic and hippocampal component) ($F_{1, 68} = 15.2$, $p < 0.001$) even after multiple comparisons correction.

Associations between regional GM differences and neuropsychological test scores

Partial correlations between neuropsychological performance and brain regions that showed lower GMV following the whole-brain VBM demonstrated significant relationships across groups between thalamus and Stroop IF, RAVLT sum, RAVLT delayed recall, RAVLT recognition and AVF after applying Bonferroni corrections. There were also three significant associations across groups between the IFG and insula and the Stroop IF and RAVLT sum and delayed recall. Within group significant associations existed between thalamus and RAVLT delayed recall in individuals with VLOSLP and no significant associations remained in the group of healthy controls (Table 3).

Discussion

Our comprehensive whole-brain VBM and SBM analysis demonstrated lower volumes in the thalamus and fronto-temporal regions, including left IFG, left insula, and hippocampus in individuals with VLOSLP. Furthermore, we found that lower thalamic GMV was associated with cognitive dysfunction in this group. Of note, we included only individuals with VLOSLP, in contrast to most previous studies, which included a mixed group of LOS and VLOSLP, thus, we provide more reliable evidence on the neurobiology of VLOSLP from a relatively homogenous sample of this diagnostic category.

Further investigation of thalamic volumes suggested specific reductions in the AV/VA nucleus, VL and MD nucleus. Volumetric changes in the thalamus and specifically the MD nucleus microstructure have already been described in first episode psychosis and in clinical high-risk adults (Cho et al., 2019). Moreover, thalamic abnormality has been found to
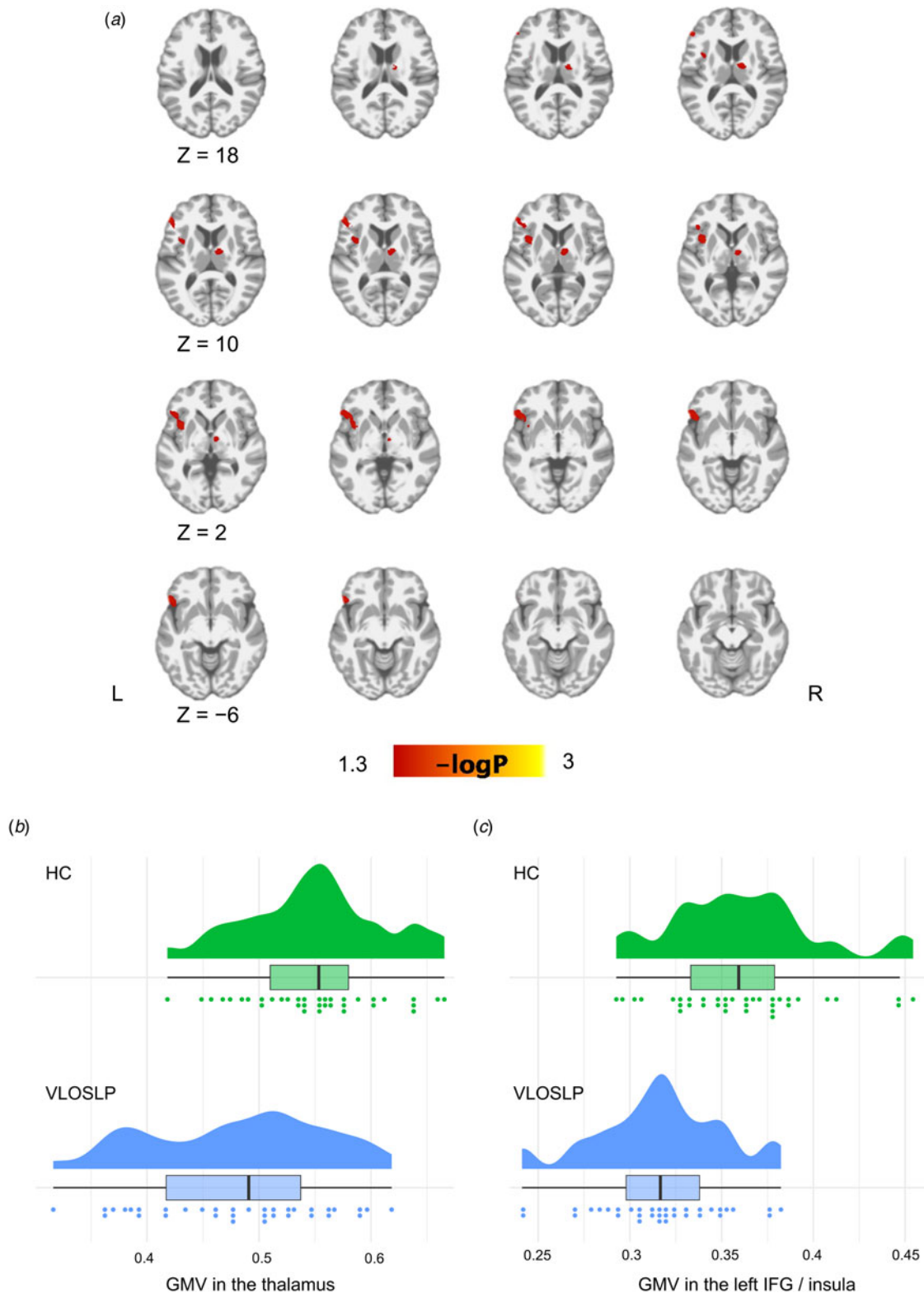
Figure 1. Lower grey matter volume in VLOSLP. (*a*) VBM showed significant grey matter volume reductions in the thalamus (*b*), inferior frontal gyrus (IFG) and insula (*c*) in individuals with VLOSLP compared with healthy controls. Significance threshold was set at family wise error corrected *p* < 0.05 determined by threshold-free cluster enhancement. '−log*p* = 1.3' is equivalent to *p* = 0.05, and '−log*p* = 3' is equivalent to *p* = 0.001.

subserve psychotic symptoms in any psychotic disorder regardless of age (Huang et al., 2020). In addition, we found lower GMV in the thalamic cluster included the areas that show structural connectivity with prefrontal and temporal regions. Prior research identified altered thalamo-cortical anatomical connectivity as a transdiagnostic feature of psychosis, already noticeable in the early stages of disease and it has also been associated with cognitive impairment (Sheffield et al., 2020).

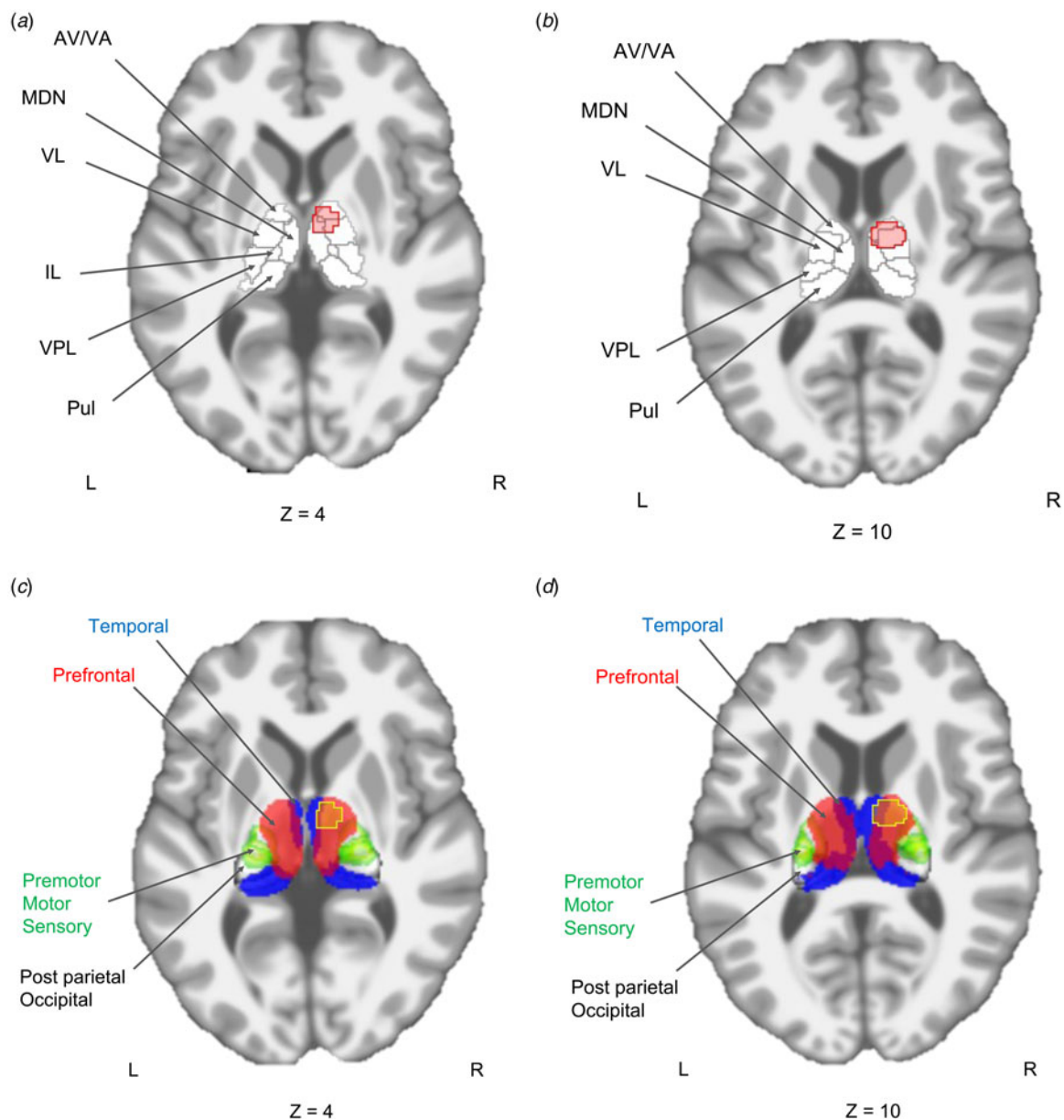**Figure 2.** Detailed exploration of grey matter volume reductions in thalamic nuclei in individuals with VLOSLP. The identified thalamic regions in the whole-brain analysis were located in the AV/VA nucleus, VL and MD nucleus according to the AAL3 brain atlas (*a, b*). These brain regions have structural connectivity with prefrontal and temporal regions according to the Oxford Thalamic Connectivity Atlas (*c, d*). AV, anteroventral (nucleus); IL, intralaminar (nucleus); MDN, mediodorsal nucleus; Pul, pulvinar nucleus; VA, ventral anterior (nucleus); VL, ventral lateral (nucleus); VPL, ventral posterolateral.

We demonstrated impairments in patients with VLOSLP compared to healthy controls on measures of processing speed, selective attention/mental flexibility, working memory, semantic fluency, verbal memory and naming. In line with our results, a potentially less impaired recognition but clearly deficient immediate as well as delayed recall/retrieval in a verbal memory task was reported in a meta-analysis on cognition in EOS (Aleman, Hijman, de Haan, & Kahn, 1999; Frangou, Hadjulis, & Vourdas, 2007). This may point to memory deficits that are (partly) mediated by executive dysfunction, possibly related to reduced volumes in thalamic regions with prefrontal and temporal connections (Doughty & Done, 2009). Such a combination of executive and memory dysfunction is also reminiscent of the two-factor model of delusions (Coltheart, 2010), which states

that the manifestation of a delusion requires the presence of memory impairment to prompt a delusional belief and coinciding executive deficits that interfere with processes of belief evaluation. Similarly, the onset of hallucinations has been linked to an interaction between problematic suppression of personal memories and impaired reality monitoring (Jellinger, 2012).

Reduced volumes in the left IFG and insula were associated specifically with impairments in mental flexibility/response inhibition as well as verbal memory across groups. Prior studies have demonstrated that a fronto-temporal network supports episodic memory (Baker, Sanders, Maccotta, & Buckner, 2001) and have also shown that the ventrolateral cortico-limbic pathway, including the IFG and insular cortex, play an important role in adapting behaviour in environmental conditions that are not always

Table 3. Partial correlations (*r* values) with age and total intracranial volume as covariates between brain volumes and neuropsychological measures across and within groups

	Thalamus across groups (VLOSLP/controls)	Left inferior frontal gyrus and insula across groups (VLOSLP/controls)
DS forward	0.094	0.099
	(0.204/−0.173)	(0.223/−0.115)
DS backwards	0.203	0.206
	(0.231/−0.109)	(0.236/−0.114)
Stroop I	−0.320*	−0.317*
	(−0.078/−0.063)	(−0.095/0.044)
Stroop IF	**−0.419***	**−0.423***
	(−0.214/−0.367*)	(−0.237/−0.138)
RAVLT sum	**0.470***	**0.442***
	(0.440*/0.129)	(0.199/0.197)
RAVLT delayed recall	**0.435***	**0.414***
	(**0.485**/0.075)	(0.275/0.202)
RAVLT recognition	**0.360**	0.307*
	(0.399*/−0.073)	(0.349*/−0.161)
AVF	**0.360**	0.259*
	(0.250/0.138)	(0.040/0.074)
BNT	0.253**	0.184
	(0.027/0.290)	(−0.039/0.126)

Notes: RAVLT, Rey Auditory Verbal Learning Test; AVF, animal verbal fluency; DS, Digit Span; BNT, Boston Naming Test; VOSP, Visual Object and Space Perception battery. * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$ before Bonferroni correction, bold print = significant after Bonferroni correction.

predictable, which is especially difficult in individuals with psychotic symptoms (Tops & Boksem, 2011). Research that looked specifically at the role of the left IFG and insula in inhibitory control, found that they were crucial even though neuroimaging studies thus far have focused more on the right IFG as a neurobiological correlate of inhibition and the left IFG has been implicated mainly in language function (Swick, Ashley, & Turken, 2008).

The large number of associations between the 'relay' structure in the brain, the thalamus, and neuropsychological results in the current study illustrates its pivotal role in memory, executive functioning as well as attention in general (Georgescu, Popa, & Zagrean, 2020; Van der Werf et al., 2003; Van der Werf, Witter, Uylings, & Jolles, 2000). Moreover, thalamic abnormalities have been associated with language, motor and executive functioning in individuals with EOS specifically (Andrews, Wang, Csernansky, Gado, & Barch, 2006; Coscia et al., 2009; Crespo-Facorro et al., 2007).

However, in the current study many of the relationships between brain volumes and neuropsychological measures were no longer significant within groups. The only significant association that remained within the group of individuals with VLOSLP was that between the thalamus and delayed recall in a verbal memory task. Verbal memory is certainly one of the more severely affected domains in schizophrenia (Frangou, 2010; Guimond, Chakravarty, Bergeron-Gagnon, Patel, & Lepage, 2015). Functional alterations to the IFG and thalamus – as detected using a proton magnetic resonance spectroscopy during a verbal learning task – have been

shown to affect verbal memory in individuals with schizophrenia, suggestive again of the importance of structural (dis)connections in cognitive impairments (Hagino et al., 2002).

A limitation of the current study is small sample size. Collecting data from larger samples is challenging in VLOSLP as the condition is rare and individuals with paranoid symptoms are often hesitant to participate in research studies. Although larger than many previous studies, the sample size may affect statistical power, possibly leading to type II errors. Indeed, our statistical threshold in the whole brain analysis and the MANCOVA comparing neuropsychological results is a standard one, which may be very strict for our sample size and lead to an underestimation of volumetric brain differences or neuropsychological deficits in VLOSLP *v.* healthy older adults. To address this issue, we therefore report the results of another VBM analysis with a liberal statistical threshold and SBM analysis, which is sensitive to group differences in small sample sizes, as supplementary analyses. Also, the limited number of significant associations between lower GMV and neuropsychological scores within groups may point to a lack of statistical power. Nevertheless, existing knowledge on the neurobiology and neuropsychology of VLOSLP is very scarce, and typically involves small groups of individuals. Moreover, previous research almost always pooled data from both LOS and VLOSLP, whereas the neurobiological mechanisms may be different in both conditions. Therefore, our findings in a larger, more clinically homogeneous sample than previous studies are relevant to the field.

Conclusion

In the current study, we found lower GMV in the left IFG and insula as well as the thalamus in individuals with VLOSLP compared with healthy older adults. The IFG, insula and thalamic areas were associated with deficits in verbal memory and executive function. Moreover, lower GMV in the thalamic cluster included the areas that show structural connectivity with prefrontal and temporal regions. Future research investigating the integrity of such structural connections could help further elucidate the neurobiological underpinnings of VLOSLP, which may identify targets for (multimodal) treatments, involving pharmacological as well as non-pharmacological revalidation approaches, promoting self-sufficiency and quality of life in individuals with VLOSLP.

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