A voxel- and source-based morphometry analysis of grey matter volume differences in Very-Late-Onset Schizophrenia-Like Psychosis

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Brain differences and neuropsychological profile in late onset psychosis

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 (IFG) 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.

Brain differences and neuropsychological profile in late onset psychosis

Keywords: late onset psychosis – neuroimaging – MRI – neuropsychology

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 characterized 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 five 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, 1992; Howard, Förstl, Naguib, Burns, & Levy; 1992; Rabins, Aylward, Holroyd, and Pearlson, 2000), greater thalamic volumes (Corey-Bloom et al., 1995), and cerebellar atrophy (Barak, Aizenberg, Mirecki, Mazeh, and Achiron, 2002).

~~Another line of research has reported a role for white matter (WM). Casanova and Lindzen (2003) suggested, based on their post-mortem research, that a significant alteration in the grey matter (GM) to WM ratio in the parahippocampal gyrus of individuals with LOS could be explained by a preservation in GM and a reduction in WM. In contrast, Howard et al. (1995) found no excess in WM hyperintensities in VLOSLP compared to healthy controls. Comparable results were reported by Rivkin et al. (2000) and Symonds et al. (1997) in LOS, leading them to suggest that WM pathology may only be a contributing factor to LOS or VLOSLP in those individuals already more prone to develop schizophrenia.~~

~~Several studies into brain function in LOS or VLOSLP have been conducted using electroencephalography, event-related potentials, positron emission tomography and single-photon emission computed tomography. These studies showed a generalized lower brain metabolism in individuals with LOS (Miyaoka et al., 2001; Miyaoka et al., 2005; Sachdev, Brodaty, Rose, & Haindl, 1997), hypo-metabolism in the frontal and temporal regions bilaterally (Olichney, Iragui, Kutas, Nowacki, & Jeste, 1997; Wake et al., 2016), and a reduced blood flow in the basal ganglia (Lesser et al., 1993).~~

~~The previous studies appear to show two types of differences in VLOSLP, one being a more diffuse and global pattern of atrophy and reduced metabolism that may be associated with (accelerated, possibly stress-related) aging and an additional pattern of reduced brain volume and hypo-metabolism in the frontal, subcortical and temporal brain regions, reminiscent of changes in EOS. Hence, it is tempting to suggest that brain ageing actually~~

~~triggers earlier (developmentally) acquired vulnerability to psychosis, which in turn may also be associated with a specific set of cognitive deficits.~~

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), 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 the 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 that show similar patterns of GM abnormalities. 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 = 9.6ms, TE = 4.6ms, flip angle = 8°, voxel-size = 0.98 × 0.98 × 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 normalization 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 utilizing independent component analysis (ICA) to identify patterns across multiple covarying networks (Xu et al., 2009). Using individual pre-processed GM image, we performed an independent component analysis (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 (Xu et al., 2009; Gupta et al., 2015), and we used the ICASSO algorithm (Himberg et al., 2004) to increase component reliability and consistency. Components with a quality index >0.9 indicating stable decomposition (Allen et al., 2011) 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 $p < .05$ 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 a supplementary material and a previous paper (Xu et al., 2009).

Neuropsychological assessments

The following instruments were administered by trained neuropsychologists in a standardized way according to published test manuals. A standardized version of the Mini Mental Status Examination (MMSE) was used as a tool for the assessment of global cognitive abilities (Folstein et al., 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 were 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 et al., 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 analyze 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 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 (FWE) corrected $p < .05$ determined by threshold-free cluster enhancement (TFCE) (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 visualize 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 $p < .05$ as the statistically significant threshold following Bonferroni correction.

~~*Supplementary analyses*~~

~~In addition to these main analyses, we also repeated the voxel-based morphometry (VBM) using a more liberal, yet standard threshold of uncorrected p=.001 at voxel-level, to allow comparison with previous work.~~ ~~Additionally, we conducted a source-based morphometry (SBM). This data-driven, multivariate extension of mass univariate VBM utilizes independent~~

~~component analysis (ICA) to identify patterns across multiple covarying networks (Xu et al., 2009). This approach requires less stringent voxel-wise multiple comparisons correction, and therefore may be more sensitive for detecting group-level GM differences in smaller samples. The results of both these analyses are reported as supplementary material.~~

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<.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 <.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 (Figure 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 (Supplementary table 1 and supplementary figure 1). ~~SBM analysis revealed lower GMV in the thalamus and hippocampal component in individuals with VLOSLP (supplementary figure 2).~~

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) 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 (Figure 2).

SBM analysis

SBM analysis identified eight stable components in our cohort (supplementary figure 2). There was a significant main effect of diagnosis on ICA loading parameters ($F_{8, 61} = 2.87$, $p = .009$). Separate univariate ANCOVAs revealed that there was a main effect of diagnosis in the component2 (thalamic and hippocampal component) ($F_{1, 68} = 15.2$, $p < .001$) 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 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).

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 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, Witter, Uylings, & Jolles, 2000; Van der werf et al., 2003). 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 versus 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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Conflicts of interest

None.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

References

Aleman, A., Hijman, R., de Haan, E. H., & Kahn, R. S. (1999). Memory impairment in schizophrenia: A meta-analysis. *The American Journal of Psychiatry, 156*(9), 1358-1366. doi: 10.1176/ajp.156.9.1358

Almeida, O. P., Howard, R., Levy, R., David, A. S., Morris, R. G., & Sahakian, B. J. (1995a). Clinical and cognitive diversity of psychotic states arising in late life (late paraphrenia). *Psychological Medicine, 25*(4), 699-714.

Almeida, O. P., Howard, R., Levy, R., David, A. S., Morris, R. G., & Sahakian, B. J. (1995b). Cognitive features of psychotic states arising in late life (late paraphrenia). *Psychological Medicine, 25*(4), 685-698.

Andrews, J., Wang, L., Csernansky, J. G., Gado, M. H., & Barch, D. M. (2006). Abnormalities of thalamic activation and cognition in schizophrenia. *The American Journal of Psychiatry, 163*(3), 463-469. doi: 10.1176/appi.ajp.163.3.463

Baker, J. T., Sanders, A. L., Maccotta, L., & Buckner, R. L. (2001). Neural correlates of verbal memory encoding during semantic and structural processing tasks. *Neuroreport, 12*(6), 1251-1256. doi: 10.1097/00001756-200105080-00039

Barak, Y., Aizenberg, D., Mirecki, I., Mazeh, D., & Achiron, A. (2002). Very late-onset schizophrenia-like psychosis: Clinical and imaging characteristics in comparison with elderly patients with schizophrenia. *Journal of Nervous and Mental Disease, 190*(11), 733-736. doi: 10.1097/01.nmd.0000038167.15155.d6

Barta, P. E., Powers, R. E., Aylward, E. H., Chase, G. A., Harris, G. J., Rabins, P. V., . . . Pearlson, G. D. (1997). Quantitative MRI volume changes in late onset schizophrenia and Alzheimer's disease compared to normal controls. *Psychiatry Research, 68*(2-3), 65-75.

Behrens, T. E., Johansen-Berg, H., Woolrich, M. W., Smith, S. M., Wheeler-Kingshott, C. A., Boulby, P. A., . . . Matthews, P. M. (2003). Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. Nature Neuroscience, 6(7), 750-757. doi: 10.1038/nn1075

Benton, A. L. (1968). Differential behavioral effects in frontal lobe disease. *Neuropsychologia, 6*(1), 53-60.

Breitner, J. C., Husain, M. M., Figiel, G. S., Krishnan, K. R., & Boyko, O. B. (1990). Cerebral white matter disease in late-onset paranoid psychosis. *Biological Psychiatry, 28*(3), 266-274.

Brichant-Petitjean, C., Legauffre, C., Ramoz, N., Ades, J., Gorwood, P., & Dubertret, C. (2013). Memory deficits in late-onset schizophrenia. *Schizophrenia Research, 151*(1-3), 85-90. doi: 10.1016/j.schres.2013.08.021

Casanova, M. F. (2010). The pathology of paraphrenia. *Current Psychiatry Reports, 12*(3), 196-201. doi: 10.1007/s11920-010-0108-8

Chen, L., Chen, X., Liu, W., Wang, Q., Jiang, T., Wang, J., . . . Tang, J. (2013). White matter microstructural abnormalities in patients with late-onset schizophrenia identified by a voxel-based diffusion tensor imaging. *Psychiatry Research, 212*(3), 201-207. doi: 10.1016/j.pscychresns.2012.05.009

Cho, K. I. K., Kwak, Y. B., Hwang, W. J., Lee, J., Kim, M., Lee, T. Y., & Kwon, J. S. (2019). Microstructural changes in higher-order nuclei of the thalamus in patients with first-episode psychosis. Biological Psychiatry, 85(1), 70-78. doi: 10.1016/j.biopsych.2018.05.019

Coltheart, M. (2010). The neuropsychology of delusions. *Annals of the New York Academy of Sciences, 1191*, 16-26. doi: 10.1111/j.1749-6632.2010.05496.x

Copeland, J. R., Dewey, M. E., Scott, A., Gilmore, C., Larkin, B. A., Cleave, N., McCracken, C. F., & McKibbin, P. E. (1998). Schizophrenia and delusional disorder in older age: Community prevalence, incidence, comorbidity, and outcome. *Schizophrenia Bulletin, 24*(1), 153-161. doi: 10.1093/oxfordjournals.schbul.a033307

Corey-Bloom, J., Jernigan, T., Archibald, S., Harris, M. J., & Jeste, D. V. (1995). Quantitative magnetic resonance imaging of the brain in late-life schizophrenia. *The American Journal of Psychiatry, 152*(3), 447-449. doi: 10.1176/ajp.152.3.447

Coscia, D., Narr, K., Robinson, D., Hamilton, L., Sevy, S., Burdick, K., . . . Szeszko, P. (2009). Volumetric and shape analysis of the thalamus in first-episode schizophrenia. *Human Brain Mapping, 30*, 1236-1245. doi: 10.1002/hbm.20595

Crespo-Facorro, B., Roiz-Santiáñez, R., Pelayo-Terán, J. M., Rodríguez-Sánchez, J. M., Pérez-Iglesias, R., González-Blanch, C., . . . Vázquez-Barquero, J. L. (2007). Reduced thalamic volume in first-episode non-affective psychosis: Correlations with clinical

variables, symptomatology and cognitive functioning. *NeuroImage, 35*(4), 1613-1623. doi: 10.1016/j.neuroimage.2007.01.048

Doughty, O. J., & Done, D. J. (2009). Is semantic memory impaired in schizophrenia? A systematic review and meta-analysis of 91 studies. *Cognitive Neuropsychiatry, 14*(6), 473-509. doi: 10.1080/13546800903073291

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12*(3), 189–198. doi.org/10.1016/0022-3956(75)90026-6

Frangou, S. (2010). Cognitive function in early onset schizophrenia: A selective review. *Frontiers in Human Neuroscience, 3*(79). doi: 10.3389/neuro.09.079.2009

Frangou, S., Hadjulis, M., & Vourdas, A. (2007). The Maudsley early onset schizophrenia study: Cognitive function over a 4-year follow-up period. *Schizophrenia Bulletin, 34*(1), 52-59. doi: 10.1093/schbul/sbm124

Georgescu, I. A., Popa, D., & Zagrean, L. (2020). The anatomical and functional heterogeneity of the mediodorsal thalamus. *Brain Sciences, 10*(9). doi: 10.3390/brainsci10090624

Girard, C., Simard, M., Noiseux, R., Laplante, L., Dugas, M., Rousseau, F., . . . Bernier, P. J. (2011). Late-onset-psychosis: cognition. *International Psychogeriatrics, 23*(8), 1301-1316. doi: 10.1017/s1041610211000238

Goodglass, H., Kaplan, E., & Weintraub, S. (1983). *Boston naming test*: Lea & Febiger Philadelphia, PA.

Guimond, S., Chakravarty, M. M., Bergeron-Gagnon, L., Patel, R., & Lepage, M. (2015). Verbal memory impairments in schizophrenia associated with cortical thinning. *NeuroImage, 11*, 20-29. doi: 10.1016/j.nicl.2015.12.010

Guo, X., Li, J., Wei, Q., Fan, X., Kennedy, D. N., Shen, Y., Chen, H., & Zhao, J. (2013). Duration of untreated psychosis is associated with temporal and occipitotemporal gray matter volume decrease in treatment naïve schizophrenia. *PloS One, 8*(12), e83679. doi: 10.1371/journal.pone.0083679

Hagino, H., Suzuki, M., Mori, K., Nohara, S., Yamashita, I., Takahashi, T., . . . Kurachi, M. (2002). Proton magnetic resonance spectroscopy of the inferior frontal gyrus and thalamus and its relationship to verbal learning task performance in patients with schizophrenia: A preliminary report. [10.1046/j.1440-1819.2002.01045.x]. *Psychiatry and Clinical Neurosciences, 56*(5), 499-507. doi: 10.1046/j.1440-1819.2002.01045.x

Hanssen, M., van der Werf, M., Verkaaik, M., Arts, B., Myin-Germeys, I., van Os, J., . . . Kohler, S. (2015). Comparative study of clinical and neuropsychological characteristics between early-, late and very-late-onset schizophrenia-spectrum disorders. *The American Journal of Geriatric Psychiatry, 23*(8), 852-862. doi: 10.1016/j.jagp.2014.10.007

Heaton, R., Paulsen, J. S., McAdams, L. A., Kuck, J., Zisook, S., Braff, D., . . . Jeste, D. V. (1994). Neuropsychological deficits in schizophrenics. Relationship to age, chronicity, and dementia. *Archives of General Psychiatry, 51*(6), 469-476. doi: 10.1001/archpsyc.1994.03950060033003

Henderson, A. S., Korten, A. E., Levings, C., Jorm, A. F., Christensen, H., Jacomb, P. A., & Rodgers, B. (1998). Psychotic symptoms in the elderly: A prospective study in a population sample. *International Journal of Geriatric Psychiatry*, *13*(7), 484-492.

Howard, R., Castle, D., O'Brien, J., Almeida, O., & Levy, R. (1992). Permeable walls, floors, ceilings and doors. Partition delusions in late paraphrenia. *International Journal of Geriatric Psychiatry, 7*, 719-724.

Howard, R., Förstl, H., Almeida, O., Burns, A., & Levy, R. (1992). Computer-assisted CT measurements in late paraphrenics with and without Schneiderian first-rank symptoms: A preliminary report. *International Journal of Geriatric Psychiatry, 7*(1), 35-38. doi: 10.1002/gps.930070106

Howard, R., Förstl, H., Naguib, M., Burns, A., & Levy, R. (1992). First-rank symptoms of Schneider in late paraphrenia. Cortical structural correlates. *The British Journal of Psychiatry, 160*, 108-109.

Howard, R., Rabins, P. V., Seeman, M. V., Jeste, D. V., & The International Late-Onset Schizophrenia Group. (2000). Late-onset schizophrenia and very-late-onset schizophrenia-like psychosis: An international consensus. *The American Journal of Psychiatry, 157*(2), 172-178. doi: 10.1176/appi.ajp.157.2.172

Huang, A. S., Rogers, B. P., Sheffield, J. M., Jalbrzikowski, M. E., Anticevic, A., Blackford, J. U., Heckers, S., & Woodward, N. D. (2020). Thalamic nuclei volumes in psychotic disorders and in youths with psychosis spectrum symptoms. *The American Journal of Psychiatry, 177*(12), 1159–1167. https://doi.org/10.1176/appi.ajp.2020.19101099

Jellinger, K. A. (2012). Cerebral correlates of psychotic syndromes in neurodegenerative diseases. *J Cell Mol Med, 16*(5), 995-1012. doi: 10.1111/j.1582-4934.2011.01311.x

Jeste, D. V., Harris, M. J., Krull, A., Kuck, J., McAdams, L. A., & Heaton, R. (1995). Clinical and neuropsychological characteristics of patients with late-onset schizophrenia. *The American Journal of Psychiatry, 152*(5), 722-730. doi: 10.1176/ajp.152.5.722

Jones, D. K., Catani, M., Pierpaoli, C., Reeves, S. J., Shergill, S. S., O'Sullivan, M., . . . Howard, R. (2005). A diffusion tensor magnetic resonance imaging study of frontal cortex connections in very-late-onset schizophrenia-like psychosis. *The American Journal of Geriatric Psychiatry, 13*(12), 1092-1099. doi: 10.1097/00019442-200512000-00009

Jones, G., & Macken, B. (2015). Questioning short-term memory and its measurement: Why digit span measures long-term associative learning. *Cognition, 144*, 1-13. doi: 10.1016/j.cognition.2015.07.009

Lesser, I. M., Miller, B. L., Swartz, J. R., Boone, K. B., Mehringer, C. M., & Mena, I. (1993). Brain imaging in late-life schizophrenia and related psychoses. *Schizophrenia Bulletin, 19*(4), 773-782.

Miller, B. L., Lesser, I. M., Boone, K. B., Hill, E., Mehringer, C. M., & Wong, K. (1991). Brain lesions and cognitive function in late-life psychosis. *The British Journal of Psychiatry, 158*, 76-82.

Miller, G. A. (1956). The magical number seven, plus or minus two: Some limits on our capacity for processing information. *Psychological Review, 63*(2), 81-97. doi: 10.1037/h0043158

Naguib, M., & Levy, R. (1987). Late paraphrenia: Neuropsychological impairment and structural brain abnormalities on computed tomography. *International Journal of Geriatric Psychiatry, 2*(2), 83-90. doi: 10.1002/gps.930020205

Östling, S., Johansson, B., & Skoog, I. (2004). Cognitive test performance in relation to psychotic symptoms and paranoid ideation in non-demented 85-year-olds. *Psychological Medicine, 34*(3), 443-450. doi: 10.1017/S0033291703001144

Rabin, L. A., Paolillo, E., & Barr, W. B. (2016). Stability in test-usage practices of clinical neuropsychologists in the United States and Canada over a 10-year period: A follow-up survey of INS and NAN members. *Archives of Clinical Neuropsychology, 31*(3), 206-230. doi: 10.1093/arclin/acw007

Rabins, P., Aylward, E., Holroyd, S., & Pearlson, G. (2000). MRI findings differentiate between late-onset schizophrenia and late-life mood disorder. *International Journal of Geriatric Psychiatry, 15*(10), 954-960.

Rabins, P., Pearlson, G., Jayaram, G., Steele, C., & Tune, L. (1987). Increased ventricle-to-brain ratio in late-onset schizophrenia. *The American Journal of Psychiatry, 144*(9), 1216-1218. doi: 10.1176/ajp.144.9.1216

Rey, A. (1964). *L'examen clinique en psychologie*. Paris.

Sachdev, P., & Brodaty, H. (1999). Quantitative study of signal hyperintensities on T2-weighted magnetic resonance imaging in late-onset schizophrenia. *The American Journal of Psychiatry, 156*(12), 1958-1967. doi: 10.1176/ajp.156.12.1958

Sachdev, P., Brodaty, H., Cheang, D., & Cathcart, S. (2000). Hippocampus and amygdala volumes in elderly schizophrenic patients as assessed by magnetic resonance imaging. *Psychiatry and Clinical Neurosciences, 54*(1), 105-112. doi: 10.1046/j.1440-1819.2000.00644.x

Sachdev, P., Brodaty, H., Roubina, S., & Mackenzie, R. A. (1999). An electroencephalographic investigation of late-onset schizophrenia. *International Psychogeriatrics, 11*(4), 421-429.

Sheffield, J. M., Huang, A. S., Rogers, B. P., Giraldo-Chica, M., Landman, B. A., Blackford, J. U., . . . Woodward, N. D. (2020). Thalamocortical anatomical connectivity in schizophrenia and psychotic bipolar disorder. Schizophrenia Bulletin, 46(5), 1062-1071. doi: 10.1093/schbul/sbaa022

Sharma, E. R., Debsikdar, A. V., Naphade, N. M., & Shetty, J. V. (2014). Very late-onset schizophrenia like psychosis: Case series and future directions. *Indian Journal of Psychological Medicine, 36*(2), 208-210. doi: 10.4103/0253-7176.130999

Smith, S. M., & Nichols, T. E. (2009). Threshold-free cluster enhancement: Addressing problems of smoothing, threshold dependence and localisation in cluster inference. *NeuroImage, 44*(1), 83-98. doi: 10.1016/j.neuroimage.2008.03.061

Strauss, E., Sherman, E., & Spreen, O. (2006). *A compendium of neuropsychological tests*: New York: Oxford University Press.

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology, 18,* 643-662.

Su, K. P., Hsu, C. Y., Hsieh, S. C., & Shen, W. W. (2001). Magnetic resonance imaging findings in patients with delusional disorder due to diffuse cerebrovascular disease: a report of seven cases. *Psychiatry and Clinical Neurosciences, 55*(2), 121-126. doi: 10.1046/j.1440-1819.2001.00798.x

Swick, D., Ashley, V., & Turken, A. U. (2008). Left inferior frontal gyrus is critical for response inhibition. *BMC Neuroscience, 9,* 102. doi: 10.1186/1471-2202-9-102

Tops, M., & Boksem, M. A. S. (2011). A potential role of the inferior frontal gyrus and anterior insula in cognitive control, brain rhythms, and event-related potentials. *Frontiers in Psychology, 2,* 330. doi: 10.3389/fpsyg.2011.00330

Vahia, I. V., Palmer, B. W., Depp, C., Fellows, I., Golshan, S., Kraemer, H. C., & Jeste, D. V. (2010). Is late-onset schizophrenia a subtype of schizophrenia? *Acta Psychiatrica Scandinavica, 122*(5), 414-426. doi: 10.1111/j.1600-0447.2010.01552.x

Van Assche, L., Morrens, M., Luyten, P., Van de Ven, L., & Vandenbulcke, M. (2017). The neuropsychology and neurobiology of late-onset schizophrenia and very-late-onset schizophrenia-like psychosis: A critical review. *Neuroscience & Biobehavioral Reviews, 83,* 604-621. doi: 10.1016/j.neubiorev.2017.08.024

Van der Elst, W., Van Boxtel, M. P., Van Breukelen, G. J., & Jolles, J. (2006). The Stroop color-word test: Influence of age, sex, and education; and normative data for a large sample across the adult age range. *Assessment, 13*(1), 62-79. doi: 10.1177/1073191105283427

Van der Werf, Y. D., Scheltens, P., Lindeboom, J., Witter, M. P., Uylings, H. B., & Jolles, J. (2003). Deficits of memory, executive functioning and attention following infarction in the thalamus: A study of 22 cases with localised lesions. *Neuropsychologia, 41*(10), 1330-1344. doi: 10.1016/s0028-3932(03)00059-9

Van der Werf, Y. D., Witter, M. P., Uylings, H. B., & Jolles, J. (2000). Neuropsychology of infarctions in the thalamus: A review. *Neuropsychologia, 38*(5), 613-627. doi: 10.1016/s0028-3932(99)00104-9

van Os, J., Howard, R., Takei, N., & Murray, R. (1995). Increasing age is a risk factor for psychosis in the elderly. *Social Psychiatry and Psychiatric Epidemiology, 30*(4), 161-164.

Xu, L., Groth, K. M., Pearlson, G., Schretlen, D. J., & Calhoun, V. D. (2009). Source-based morphometry: The use of independent component analysis to identify gray matter differences with application to schizophrenia. *Human Brain Mapping, 30*(3), 711-724.

Zakzanis, K. K., Kielar, A., Young, D. A., & Boulos, M. (2001). Neuropsychological differentiation of late onset schizophrenia and frontotemporal dementia. *Cognitive Neuropsychiatry, 6*(1), 63-77. doi: 10.1080/13546800042000052

Figure legend

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. "–logP = 1.3" is equivalent to $p = 0.05$, and "–logP = 3" is equivalent to $p = 0.001$.

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).

Abbreviations: AV, anteroventral (nucleus); IL, intralaminar (nucleus); MDN, mediodorsal nucleus; Pul, pulvinar nucleus; VA, ventral anterior (nucleus); VL, ventral lateral (nucleus); VPL, ventral posterolateral.