The neuropsychology and neurobiology of late-onset schizophrenia and very-late-onset schizophrenia-like psychosis: a critical review

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Abstract

Objective: The current review discusses neuropsychological profiles and the longitudinal course of cognitive dysfunction in Late Onset Schizophrenia (LOS) and Very-late-onset schizophrenia-like psychosis (VLOSLP), and attempts to clarify its neurobiological underpinnings. **Method**: A systematic literature search resulted in 29 publications describing original research on the neuropsychology of LOS/VLOSLP and 46 studies focussing on neurobiology. **Results**: Although mildly progressive cognitive impairment is usually present, only a subgroup of LOS/VLOSLP develops dementia during a 10-year follow-up succeeding the onset of psychosis. This coincides with the absence of neuropathological evidence for neurodegeneration in many cases. Cognitive deterioration is characterized by deficits in (working) memory, language, psychomotor speed and executive functioning. Underlying neurobiological changes encompass white matter pathology, increased ventricle-to-brain ratio (VBR) with coinciding atrophy and hypo-metabolism of frontal, temporal and subcortical areas. **Conclusions**: Multiple changes in neurobiology and cognition contributing to LOS/VLOSLP may reflect stress-related accelerated brain aging rather than neurodegenerative pathology. Their involvement in the onset of illness, however, might be inversely proportional to pre-existing (psychosocial and/or genetic) vulnerability to psychosis.

Keywords: elderly, schizophrenia, neuropsychology, neurobiology

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Although schizophrenia is generally considered as a disease with onset in adolescence, several studies report on individuals who first experienced psychotic symptoms in late life in the absence of a mood disorder or neurological illness [1-3]. An international expert consensus referred to psychosis with an onset after 40 years of age as late-onset schizophrenia (LOS). Very-late-onset schizophrenia-like psychosis (VLOSLP) was delineated as a condition with onset of psychotic symptoms after 60 years [2]. Although these age ranges seem arbitrary, they result from expert discussion and are hypothesized to reflect differing subtypes of schizophrenia-like illnesses with separate mechanisms contributing to onset and maintenance of symptoms [2, 4].

The one-year prevalence of schizophrenia in individuals aged 45 to 65 years is 0.6% [5], whereas the community prevalence for VLOSLP ranges from 0.1% to 0.5% [2]. However, in two samples of 8010 Dutch and 1777 British patients aged 60 years or older who were admitted to hospital, there was a linear trend in the association between increasing age and first onset of non-organic, non-affective psychosis. Specifically, the annual incidence of VLOSLP increased by 11% with each 5 year increase in age [6]. As the older age groups are the fastest growing segment in the world population, healthcare may thus increasingly be confronted with a first episode of psychosis in elderly patients. Hence, research into this highly incapacitating disorder is needed. Even more so as prior studies suggest that research on schizophrenia with onset before the age of 45 years (Average age Onset Schizophrenia, AOS), is not always generalizable towards LOS or VLOSLP. For instance, in contrast with AOS, there is a female preponderance in VLOSLP and LOS [2]. Furthermore, there is a lower morbid risk in relatives of individuals with VLOSLP in comparison with AOS, suggesting a

lower genetic risk factor for LOS/VLOSLP [7]. Finally, clinical features differ, with the most striking differences between AOS and VLOSLP [8]. VLOSLP is characterized by positive psychotic symptoms such as delusions and (multimodal) hallucinations. Specifically, partition delusions – concerning the unwanted permeability of borders – and paranoid delusions are highly prominent [9]. On the other hand, formal thought disorder is usually absent. Furthermore, there are fewer negative symptoms such as affective flattening in VLOSLP and LOS compared to AOS [2]. These findings regarding epidemiology and phenomenology point to (partly) diverging etiological mechanisms in AOS and VLOSLP. They may also be associated with different cognitive profiles, as for instance negative symptoms and disorganization are related to executive dysfunction more often than reality distortion in AOS [10]. Moreover, female predominance may mask group differences with respect to social cognition between AOS and LOS/VLOSLP as there are known gender differences in social cognition in healthy controls, suggesting better performance in females [11].

Some researchers have disputed the diagnostic validity of LOS or VLOSLP [12, 13]. They suggest that particularly VLOSLP encompasses a prodromal phase of a neurodegenerative disease such as Alzheimer's disease (AD) with predominantly memory (and language) dysfunction [14, 15], frontotemporal degeneration (FTD) with important executive dysfunction and impaired social cognition in the behavioral variant [16], or dementia with Lewy bodies (LBD) which is initially primarily characterized by perceptual and executive deficits [17] according to systematic review and/or meta-analysis. Neurodegenerative illnesses are certainly more prevalent in late life and are often accompanied by behavioral and psychological symptoms, such as depression or psychosis [18]. Moreover, these symptoms may occur before cognitive decline becomes apparent. Coincidently, mild cognitive impairment (MCI) is frequently observed in LOS and VLOSLP, thus creating an overlap in clinical presentation of LOS or VLOSLP and neurodegenerative disorders.

Still, research has shown that VLOSLP, though it may be associated with an increased risk of dementia compared to normally aging older adults [19], does not invariably predict cognitive or functional decline [20, 21]. In many cases there is a non-progressive dysfunction, reminiscent of the static encephalopathy of AOS. Nevertheless, in late life a static cognitive dysfunction accompanied by psychotic symptoms might not only represent a (latent) neurodevelopmental disorder surfacing as a result of environmental triggers, it is possibly combined with stress-related accelerated neurobiological ageing which may increase pre-existent vulnerability to psychopathology. Finally, non-progressive cognitive impairment in later life is often also associated with cerebrovascular disease.

Differential diagnosis between an incident dementia or a static (neurodevelopmental and/or cerebrovascular) encephalopathy in late onset psychosis is valuable with respect to early treatment possibilities. Neuropsychological assessment is one possible non-invasive and sensitive diagnostic tool that may provide insight into the characteristic cognitive and related neurobiological profiles in LOS and VLOSLP as opposed to neurodegeneration [10, 22], and it may also further our understanding of the (socio)cognitive and neurobiological mechanisms that cause an onset of psychosis in late life and sustain it [10, 23]. However, common clinical practice mostly utilizes neuropsychological assessment in conjunction with functional or structural brain imaging as proper diagnostic research encompasses information from different and compatible sources [24]. Whereas neuropsychological assessment is usually conducted for the purpose of differential diagnosis, prediction of functional potential, and measuring treatment response or disease course, clinical correlation with imaging findings can be complementary as imaging studies can specify the location of many structural and functional brain changes leading to cognitive changes [25]. Notably, correlations may sometimes be low or absent as imaging brain changes can be associated with nearly normal cognitive functioning due to compensatory neurological mechanisms, while individuals with

no lesions detectable on imaging can have substantial cognitive and functional limitations, leading to the suggestion that neuropsychological research may sometimes detect subtle disease-related changes before these become apparent on imaging [25]. In summary, neuropsychological research allows for quantitative descriptions of the patient's cognitive status, and combined with imaging results it may increase our understanding of brain–behaviour relationships [24]. However, there have been little studies directly correlating neuropsychological results with imaging research, electro-encephalogram (EEG) or event related potential (ERP) in LOS or VLOSLP.

In the current review, we will therefore first try to identify a neuropsychological profile which is characteristic of VLOSLP or LOS. Additionally, we will look at research concerning its typical evolution and possible underlying neuroanatomical or functional changes. We will review study results and implications for clinical practice. To conclude, we will suggest possibilities for future research.

Method

A systematic literature search was conducted in Pubmed and Limo using the search terms 'very-late-onset schizophrenia-like psychosis', 'late-onset schizophrenia', 'late-onset psychosis', 'late paraphrenia' and 'paraphrenia' in combination with 'cognition', 'cognitive', 'neuropsychology' or 'neuropsychological' and subsequently in combination with 'neurobiology', 'imaging', 'neural', 'atrophy', 'white matter', 'grey matter' and 'neuroanatomy'. We used the term '(late) paraphrenia' as it refers to a group of individuals with late onset psychosis or delusional disorder (> 50 years) without deterioration of personality or intellect. Hence, the concept partly overlaps with LOS and VLOSLP and has often been replaced by the latter diagnostic categories in recent research as a result of the expert consensus in 2000 [2, 26]. Articles were manually screened for relevancy. Only

original research was withheld for the current review. Exclusion criteria were a language of publication other than English, Dutch, German or French. The literature search resulted in 24 relevant publications on cognition in LOS and VLOSLP. References of retrieved papers were hand searched which led to an additional five studies. There were 46 studies on the neurobiology of LOS and VLOSLP, also including two case studies which will not be discussed because the patients showed comorbidity that might have influenced results. Importantly also, some studies analyzed data from the same or an overlapping participant sample (UCSD Late Life Schizophrenia research program). Therefore, we will not treat all of the retrieved articles as separate research findings. Finally, the great diversity in study design and assessment measures necessitated a systematic review instead of a meta-analysis.

Neuropsychology in LOS/VLOSLP

The first part of the review consists of an extensive summary of neurocognitive changes in late and very late onset schizophrenia-like illnesses. We will discuss (socio)cognitive profiles of LOS and VLOSLP in comparison with normally aging individuals, adult onset schizophrenia and neurodegeneration. First, cross-sectional data will be summarized (Table 1). Next, the longitudinal course of (socio)cognitive functioning will be enlightened (Table 2). In a second part of the review, there will be an in-depth discussion of neurobiological findings in LOS and VLOSLP. Findings from these two lines of research are then integrated in the conclusions subsection.

General cognitive abilities. A comparison of the neuropsychological profile in LOS and VLOSLP versus normally aging individuals permits to level out the effects of age on cognition in determining a cognitive profile of LOS/VLOSLP. Specifically, processing speed and executive function show mild decreases in non-pathological brain aging [27]. Episodic memory shows a decline with respect to learning and free recall, though consolidation

remains preserved. In light of these changes occurring in normally aging individuals, it is interesting to note that the majority of studies found impairment in general cognitive function in LOS/VLOSLP as opposed to healthy controls [28-33]. There were only three exceptions. In one small study by Phillips, Howard and David [23] three cases of VLOSLP and eight controls were compared, which yielded no clear differences in Mini Mental State Examination (MMSE) scores. Coincidently, another relatively small study by Girard et al. [34] found no significant differences in basic cognitive functioning of LOS/VLOSLP (n=15) and healthy controls (n=11). Thirdly, Almeida and colleagues [28, 29] used factor analysis and showed that within their mixed group of LOS/VLOSLP, of which the total group exhibited difficulties, there were actually two subgroups. A first subgroup displayed restricted executive deficits and the other group showed a generalized cognitive dysfunction. The first cluster had severe psychotic symptoms, whereas the second cluster exhibited more pronounced neurologic signs, such as tardive dyskinesia. Importantly, there was no significant difference between both clusters concerning age, age at onset or duration of illness. In summary, even though there is a large heterogeneity within the groups, the majority of individuals with late or very late onset schizophrenia-like illness show a cognitive impairment that exceeds the expected decline non-pathological aging.

Furthermore, a systematic screening of studies that looked into cognition in (mostly) older AOS subjects as opposed to LOS and VLOSLP participants, showed comparable performances in AOS and LOS or mixed groups of LOS and VLOSLP [32, 34-36], which we would expect if LOS and VLOSLP are disorders related to AOS. Only one exception to a general consensus of an overlap in AOS and LOS/VLOSLP was found. Sachdev, Brodaty, Rose and Haindl [37] observed inferior performances in a mixed group of LOS and VLOSLP compared with AOS. Hanssen et al. [9], finally, noticed greater impairment in LOS as opposed to VLOSLP. These findings would suggest that LOS and VLOSLP might show

deficits that are comparable to those in other schizophrenia with adult onset and that may slightly be aggravated by age-related declines. Importantly, differences in cognitive profile have been described in chronic adult onset schizophrenia as opposed to first episode psychosis. Recent meta-analyses concluded that in chronic AOS, whereas all domains are affected, processing speed and working memory are most impaired [38]. These are often related to negative symptoms and disorganization. Furthermore, speed of processing in combination with social cognition best distinguishes schizophrenia patients from controls. Notably, several aspects of social cognition are impaired [39]. First episode psychosis, conversely, is specifically associated with reduced processing speed and verbal learning according to a recent meta-analysis [40]. Moreover, research on AOS has shown that the prodromal phase and first onset of psychosis in adulthood or childhood may cause a deterioration in some cognitive domains, which might be followed by a relative stability and a slight recuperation, sometimes during remission or after treatment with antipsychotic medication [41]. Even though many cognitive domains have a favorable response to antipsychotic medication, semantic fluency and confrontation naming do not improve as a result of treatment and are therefore considered to be a cognitive endophenotype of schizophrenia by the authors [42]. Moreover, age has been described as a potential moderator of the quality and quantity of cognitive impairment in schizophrenia with adult onset [43-45]. Specifically, older individuals with AOS have been shown to have more cognitive impairment, mainly related to intellectual capacities, attention, executive function, motor skills, perception, processing speed and memory [45]. Therefore, we may expect to see gradual but minor decline in certain cognitive domains in long term follow-up of LOS and VLOSLP.

Finally, as LOS and VLOSLP cannot consistently be associated with the onset of dementia, we do not expect to see a cognitive decline that is as prominent as the deterioration

observed in neurodegenerative disorders. Furthermore, it may be informative for clinical practice to learn whether there are specific cognitive profiles that predict a conversion to dementia or a relative stability in cognitive functioning. Research on the characterization of cognitive function in neurodegenerative conditions compared to mixed groups of LOS and VLOSLP has mainly focused on AD [46-49] and (the behavioral variant of) FTD [22]. Also, vascular cognitive impairment (VCI) with concomitant psychosis was studied [48]. Differential diagnosis with respect to LBD has not yet been the topic of research. As research is focused on selective impairments, resulting in profiles that might potentially differentiate several pathological conditions in individuals with late onset psychosis, one would expect a comparison between profiles of individuals that show a globally comparable level of functioning, e.g. as assessed using a MMSE. However, not all research included groups matched with respect to general cognitive abilities. Only Harris, Kotsopoulos and Yamin [50] compared MMSE scores and estimated premorbid intelligence using NART, and found no significant differences in a population of individuals with late onset delusional disorder and Alzheimer's disease. Heaton and colleagues [46] included participants with comparable IQ scores diagnosed with either Alzheimer's disease or schizophrenia with a young age and early onset, an old age and early onset, or with an old age and late onset. Hopkins and Roth [48], Palmer et al. [47] and Zakzanis et al. [22, 49] – comparing cognitive profiles of LOS/VLOSLP with those of Alzheimer's disease, vascular cognitive impairment and frontotemporal dementia – did not correct for general level of cognitive function. Hence, the current results on cognitive subdomains may not adequately describe selective impairments that aid differential diagnosis between LOS/VLOSLP or neurodegeneration. Replication is necessary, using groups matched with respect to general level of cognitive functioning.

Intelligence. Interestingly, studies have quite consistently described a reduced intellectual capacity in LOS or VLOSLP compared with normal controls [28, 32, 46, 51-54]. Premorbid

intelligence, however, appeared within the average range for both clinical and control groups [23, 28, 31, 35]. Notably, many studies did not assess premorbid intelligence because this was a primary research focus, but rather as a covariate. The only exceptions to these findings of an average premorbid intellectual level are the studies by Sachdev et al. [37, 53] pointing to slightly lower premorbid intelligence in LOS/VLOSLP compared with normal controls. Importantly though, participant groups partly overlapped so there was no replication of findings. Also, the authors selected a group of individuals with onset of psychotic symptoms after the age of 50. Therefore, differences between LOS and VLOSLP may have been masked. Still, it is reasonable to assume that an intellectual deterioration seems to co-occur with the onset of psychotic symptoms in late life.

The rate of intellectual decline seems comparable to that in AOS. Admittedly, only one study looked into premorbid intelligence in a mixed group of LOS and VLOSLP compared to older AOS subjects and found no significant difference [53]. Studies that compared LOS and VLOSLP to young and older AOS also found similar current intellectual capacities [9, 32, 46]. This reflects a comparable decrease in intellectual capacities in all schizophrenia-like illnesses.

As expected, this deterioration seems less pronounced than that in neurodegeneration. One study found reduced performance on Matrices, an estimate of performance IQ, in VCI as opposed to a group of 31 VLOSLP and one LOS subject [48]. Moreover, Information also appears deficient in VCI compared to this group of LOS/VLOSLP subjects. Performance on a Vocabulary test, which may also be associated with verbal intelligence, is comparable in VCI and LOS/VLOSLP [48]. Senile psychosis (a neurodegenerative condition, not further specified) led to inferior test results on all three tasks compared with LOS/VLOSLP [48]. Zakzanis and colleagues [22] calculated effect sizes and report that WAIS Vocabulary,

Information and Comprehension show more impairment in LOS as opposed to FTD, suggesting a lower verbal intelligence in LOS compared to FTD.

Processing speed. Studies have thus far consistently shown impairment in LOS and VLOSLP compared to healthy controls on several aspects of processing speed, including cognitive speed, (psycho)motor speed and complex perceptual-motor speed [31-33, 46, 53-55]. Impairments are similar to those noticed in AOS for motor speed [32], information processing speed [53] and complex perceptual-motor speed [46]. Still, Vahia and colleagues [54] observed better performances in LOS as opposed to AOS. It is unclear what caused this discrepancy as samples and instruments appeared comparable. Processing speed was not explicitly compared between groups of LOS or VLOSLP and neurodegenerative conditions.

Attention. Attention – mainly referring to the spatial or auditory attention span and vigilance – shows impairment in LOS/VLOSLP compared to healthy controls [9, 28, 46, 53, 56]. Furthermore, a cross-sectional study comparing attention in AOS, LOS and VLOSLP found significantly more impairment on vigilance in VLOSLP participants compared with LOS [9]. AOS performed slightly better than VLOSLP which resulted in non-significant differences in performance when comparing AOS with both LOS and VLOSLP. Other aspects of attention, however, appeared similarly impaired in all schizophrenia-like illnesses [9, 32, 35, 46, 53]. A comparison with neurodegenerative conditions showed that FTD subjects performed significantly better on the auditory attention span compared with LOS [22]. However, the authors state that these differences were not sufficient to distinguish both disorders.

Executive function. Most studies have also described executive dysfunction in LOS or VLOSLP compared to normal controls. For instance, working memory is impaired in both LOS and VLOSLP [28, 51, 53, 56]. Furthermore, cognitive flexibility and abstraction are deficient in studies that included LOS or a mixed group of LOS and VLOSLP [32, 34, 46,

53]. Concurrently, logical reasoning shows impairment in VLOSLP [52], although Phillips and colleagues [23] noticed only deficits in his sample of three individuals with VLOSLP when the emotional content of reasoning problems was increased. Shifting and planning was consistently reduced in studies that included a mixed group of both LOS and VLOSLP [28, 29, 32]. Verbal fluency is also reported to be impaired in LOS and a mixed group [28, 56]. Still, Almeida and colleagues [29], who had distinguished two clusters within their group of individuals with LOS or VLOSLP, state that in the first cluster, with little evidence of cerebrovascular brain disease, there is merely a planning and shifting deficit compared to normal controls. Moreover, a more recent study used the Frontal Assessment Battery (FAB) to screen for sensitivity to interference, conceptualization, inhibitory control and environmental autonomy, and found no differences in performance in LOS compared to healthy controls [35]. However, the FAB, as it is a screening tool, may exhibit less sensitivity for executive dysfunction than other neuropsychological measures. So these findings may merely point to the absence of gross pathology with respect to executive function in LOS. To conclude, there is evidence to assume that several aspects of executive functioning are impaired in individuals with late or very late onset schizophrenia-like illnesses compared with normally aging individuals.

Moreover, there is relatively consistent impairment in AOS, LOS and VLOSLP with respect to executive function. Specifically, abstraction, cognitive flexibility, shifting, and working memory appear similarly reduced in AOS, LOS, VLOSLP or mixed groups [9, 32, 35, 46, 53]. However, some researches have reported superior performance of LOS compared to AOS on working memory, phonemic fluency, abstraction and cognitive flexibility with fewer perseverative mistakes in LOS or a mixed group than AOS [32, 54, 56]. Hence, executive dysfunction seems to be a core deficit in schizophrenia irrespective of the age of onset, though it might be more pronounced in AOS because of neurodevelopmental

alterations and in VLOSLP possibly because of more pronounced age-related neurobiological decline. Lastly, executive function seems differentially impaired in LOS/VLOSLP as opposed to neurodegenerative conditions. Specifically, shifting shows greater impairment in a mixed group of LOS/VLOSLP than AD [49]. On the other hand, FTD subjects scored worse on abstraction, cognitive flexibility and verbal fluency than LOS subjects [22].

Verbal/visual learning and memory. Studies with respect to learning and consolidation of verbal or visual information have yielded mixed results. Naguib and Levy [55] observed an impairment in memory and orientation in VLOSLP participants compared with healthy older adults. Later studies assessing subdomains of memory function pointed specifically to difficulties in verbal or visual learning and consolidation in LOS and mixed groups as opposed to normally aging individuals [28, 32, 33, 53, 54, 56]. Additionally, Henderson et al. [31] have reported impairment in a mixed group of LOS/VLOSLP on episodic memory, using the Episodic Memory Test (EMT). However, Girard et al. [34], in a relatively small sample, did not find impairment on verbal learning or consolidation in a comparable mixed group. Similarly, Heaton et al. [46] and Östling et al. [52] reported no significant differences in performance on verbal and visual memory tests in their samples of LOS and VLOSLP subjects respectively. Another study confirmed these findings in LOS as they found no significant impairment on the Rey Complex Figure (RCF) [56]. Interestingly, Almeida and colleagues [29] found impaired memory in the subgroup of LOS and VLOSLP participants who also showed more neurologic symptoms, whereas this impairment was absent in the other subgroup. In summary, the evidence for memory dysfunction in LOS and VLOSLP in comparison with normal aging is not entirely consistent, although the majority of studies does point to an impairment.

In line with this, a visual or verbal encoding and consolidation deficit has often been observed in AOS [57] as well as LOS and VLOSLP [9, 46, 53]. Some researchers found a

superior performance in LOS and mixed groups compared to AOS with respect to immediate recall [34, 56] or delayed recall [32]. Vahia et al. [54] have reported a better verbal memory function in LOS as opposed to AOS. There are no studies pointing to the opposite, a better performance on memory tasks in AOS compared with LOS/VLOSLP. Hence, memory dysfunction appears less severe in late onset psychosis than in AOS.

Depending on the etiology of the neurodegenerative condition, differences and similarities have been found in comparison with LOS and VLOSLP. Zakzanis and colleagues [49] found a superior performance in AD subjects as opposed to a mixed group of LOS or VLOSLP participants on most aspects of memory except for delayed recall. In line with this, Harris, Kotsopoulos and Yamin [50] found greater consolidation deficits for visual and verbal information in AD as opposed to VLOSLP. Heaton et al. [46] had already reported similar results after comparing LOS and AD. Moreover, they found less efficient learning in AD as opposed to LOS. Zakzanis et al. [49], to the contrary, observed a better immediate recall in their AD subjects as opposed to their mixed group of LOS/VLOSLP. Hence, there is inconsistency in the observations concerning learning in AD and LOS or VLOSLP, whereas consolidation seems consistently more impaired in AD than in LOS/VLOSLP. Finally, only one study compared LOS subjects to a group of individuals with FTD [22]. It showed no significant difference regarding memory function. As FTD is not typically characterized by memory dysfunction in the initial stages of the illness, and LOS/VLOSLP seems to be associated with learning deficits and sometimes consolidation difficulties compared to healthy older adults, this finding may seem counterintuitive. However, possibly, executive deficits may interfere with efficient learning and recall or recognition in FTD as well as LOS/VLOSLP, leading to stagnation in learning and inefficient recall as well as false positive recognition related to source monitoring deficits. Also, the basic level of cognitive

functioning may have been more reduced in FTD subjects compared with LOS/VLOSLP as the authors did not match their groups.

Language. Surprisingly, considering that disorganised speech and formal thought disorder are core features of schizophrenia, only three studies looked into language function in LOS and VLOSLP compared to normally aging adults. They all showed impairment. Heaton et al. [46] observed reduced confrontation naming in a mixed group of LOS/VLOSLP. Additionally, there was impairment in a similar group on the Aphasia Screening Examination which focusses on comprehension as well as speech [32]. Finally, Vahia's study including community dwelling 85 year olds found significant differences in performance in psychotic versus non-psychotic individuals on a synonym test [54]. Though these preliminary results show no inconsistency and current evidence points to impairment, especially with respect to the semantics of a language, not all aspects of language function have clearly been looked into, such as possible grammatical or pragmatic changes. Language impairment seems comparable in schizophrenia with adult and later onset. Specifically, Heaton et al. [46] and Jeste et al. [32] found no differences in verbal abilities after comparing a mixed group of LOS and VLOSLP to younger and older AOS subjects. However, clearly, these findings need replication. Studies have thus far not observed clear differences in verbal abilities when comparing LOS to AD [46], suggesting that language impairment in LOS/VLOSLP is comparable to that typically observed in AD. There is, however, a lack of research comparing language function in FTD or other neurodegenerative conditions and LOS or VLOSLP.

Perception and visuoconstruction. Research regarding visuoconstruction showed inconsistent impairment in VLOSLP and a mixed group of LOS and VLOSLP compared with normal controls [34, 52]. Östling et al. [52] report that community dwelling 85-year olds with paranoid ideation and psychotic symptoms do not perform worse on the Identical Forms

Test than 85-year olds without these symptoms. However, another study has observed difficulties in Block Design and Picture completion in a clinical group of LOS compared to healthy controls [54]. Concurrently, impairments with respect to spatial relation perception, auditory and tactual perception have been noticed in LOS and VLOSLP [23, 32, 46]. Phillips, Howard and David [23], in his small sample of three individuals with VLOSLP, has specifically observed difficulties in the matching of unfamiliar faces. Also, silhouette recognition appeared deficient. Other subtasks from the Visual Object and Space Perception (VOSP) battery showed no impairments. Admittedly, they included only a small sample of three VLOSLP participants and eight controls. Moreover, Heaton et al. [46] and Jeste et al. [32] have used data from an overlapping sample of participants. Hence, current evidence pointing to a visuospatial construction impairment in LOS and VLOSLP compared with normal aging is inconsistent, which may be partly due to the complexity of many tasks assessing visuoconstruction. Several other mental capacities, such as planning, attention or the recall of (semantic) concepts, are needed to successfully complete drawing tasks. Therefore, refinement in the assessment measures and replication of research findings is needed.

Preliminary research has, however, relatively consistently pointed to similar impairments in perception and visuoconstruction in AOS and a mixed group of LOS/VLOSLP [32, 53]. One study noticed a superior performance in LOS compared with AOS subjects on Block design, but not on Picture completion [54]. In comparison with neurodegenerative illnesses, finally, superior and inferior performances have been described, depending on the etiology of the neurodegeneration or the specific visuoconstructive or perceptual skill. One study has pointed to inferior performances on visual-perceptual organization in LOS compared with FTD [22]. There were no clear differences in performance on perceptual tasks when comparing LOS with AD in one study [46]. Still, Harris, Kotsopoulos and Yamin [50] did

observe impairment in visuoperceptual skills, specifically object recognition, in VLOSLP compared with AD subjects.

Social cognition. Phillips et al. [23] were the first to research facial affect recognition in three individuals with VLOSLP and they found no impairment. More recently, another study used a set of six stories devised by Snowden et al. (unpublished) as a verbal and perhaps cognitively more challenging mentalizing task [51]. The researchers also investigated probabilistic reasoning with the Beads-in-a-Jar task. Findings showed no significant differences in VLOSLP, late-onset depression (LOD) and healthy older controls with respect to probabilistic reasoning. Mentalization tasks yielded only one significant difference in performance. Whereas first- and second-order beliefs were generally accurate, performance on deception mentalizing tasks appeared more impaired in VLOSLP than in LOD and healthy controls. Finally, Smeets-Janssen et al. [35] studied theory-of-mind using a Hinting Task. They found that individuals with LOS scored comparable to healthy controls. In summary, studies have thus far shown no severe or global impairment in social cognition in LOS or VLOSLP compared with non-pathological aging. Only one study comparing social cognition in LOS and AOS was found and it showed significantly lower scores on the Hinting task in AOS compared with LOS, suggesting a more impaired theory of mind in the AOS group [35]. Surprisingly, social cognition has not been studied in groups of LOS and VLOSLP compared to neurodegenerative conditions. However, this might be an aspect of cognitive function which can potentially distinguish between LOS or VLOSLP and for instance a behavioral variant of FTD as the latter has been found to show clear impairment in social cognitive abilities [58].

In summary, the (socio)cognitive profile of LOS and/or VLOSLP may be characterized by more pronounced decline in the domains of processing speed, executive control, memory and

language compared to normally aging individuals. With respect to language, there is evidence for changes in the semantics of language function, both in receptive skills and in production. Syntax or pragmatics have not been investigated. Finally, only in a clinical group of LOS or VLOSLP – compared with a non-clinical community dwelling population of older adults with psychotic symptoms – is there impairment in visuoconstruction and perception. However, these findings are inconsistent. Assessment measures need further refinement and results clearly need replication.

The cognitive profile of LOS and VLOSLP also shows the characteristic reduced psychomotor speed that has been observed in AOS. However, executive and memory dysfunction seem less severe, though VLOSLP subjects are more impaired with respect to vigilance according to the only study that directly compared AOS and LOS to VLOSLP [9]. Also, social cognition appears to show less impairment. Still, other cognitive domains, such as language and perception, might be similarly affected in late life. Hence, a diffuse but milder cognitive dysfunction characterizes LOS and VLOSLP compared to AOS. As there are cognitive domains which seem (more or) less related to the presence or intensity of psychotic symptoms in AOS, findings pointing to pathology in LOS and VLOSLP that is milder but also more diffuse may indicate that deficits in certain domains - specifically those domains that seem relatively spared in AOS - result from (stress-related accelerated) brain aging rather than the onset of psychosis in late life.

Compared with neurodegenerative conditions, finally, there are superior and inferior performances in LOS and VLOSLP depending on the specific etiology of neurodegeneration. Although both LOS/VLOSLP and AD are associated with memory deficits, consolidation is more severely impaired in AD compared with LOS or VLOSLP. Language deficits are comparable in both conditions. Furthermore, executive deficits in FTD and LOS/VLOSLP differ with FTD showing more impairment in flexibility, abstraction and fluency. FTD

subjects, however, perform better on auditory attention span compared with VLOSLP. Both conditions may be characterized by similar memory dysfunction, typically associated with inefficient learning and recall as well as recognition, most likely secondary to executive deficits. Although social cognition may prove informative with respect to differential diagnosis, there are currently no studies investigating this domain in LOS/VLOSLP compared with neurodegenerative conditions. Finally, there is a lack of research on LBD compared to LOS/VLOSLP.

Longitudinal course of cognitive function in LOS/VLOSLP

Longitudinal research comparing LOS and VLOSLP with normally aging individuals, AOS or neurodegeneration has ranged in follow-up period from several months to ten years. All studies have used either cognitive screening instruments, an informant interview or clinical rating scales, specifically the Clinical Dementia Rating (CDR) (see Table 2). Hence, assessments lack specificity and are sometimes based on indirect report rather than a direct measurement of abilities. Although an indirect assessment of cognition may show a bias, it might also compensate for the impairment found using test instruments in a population that is not very willing or motivated to participate in research. Hence, converging study results may increase the validity of findings.

In general, studies confirm that there is a stable pattern of cognitive performance in mixed groups of LOS and VLOSLP compared with normal aging after a one or two-year interval [13, 47, 59]. However, Hymas, Naguib and Levy [60] have reported a cognitive decline in both VLOSLP and healthy controls after 3.7years. Still, the decline was greater in VLOSLP. Concurrently, Brodaty et al. [13] have observed a cognitive decline in a mixed group of LOS/VLOSLP after a follow-up period of 5years. They report that 47.4% of their subjects developed dementia, mostly associated with Alzheimer’s disease. Holden [61] states that in

subjects that developed dementia at a ten year follow-up, cognitive impairment was already more prominent at baseline assessment compared to VLOSLP subjects who did not develop dementia. Hence, it is likely that a subgroup of individuals with LOS or VLOSLP are actually experiencing the first symptoms of dementia at baseline assessment. Research into the longitudinal course of cognition in LOS/VLOSLP compared with neurodegenerative conditions has indeed shown a relative stability in a mixed group of LOS/VLOSLP as opposed to a steady decline in AD after one and two years [47]. Importantly, the presence of psychosis in AD did not affect the longitudinal course of cognitive functioning. The longitudinal course of cognition in FTD, LBD and VCI compared to LOS or VLOSLP has, however, not been studied yet.

Consistent with these findings, the longitudinal course of cognitive function appears not clearly progressive in a mixed group and in VLOSLP (with onset of psychosis after 70 years) as well as in AOS [47, 62] with follow-up periods that were relatively short, as they ranged from six months to two years. However, again, only screening instruments assessing general cognitive ability have been used or a telephone interview with primary caregivers, which may lead to insufficient sensitivity to detect changes in separate cognitive domains.

Neurobiology of LOS and VLOSLP

In the second part of the current review we will discuss the possible neurobiological underpinnings of the observed neurocognitive deficits, which seem to be most consistently present in the domains of processing speed, attention and executive function, memory and language. The impairments are typically comparable to or more limited than those in AOS. However, learning deficits are comparable to those in FTD and AD, whereas consolidation appeared more reduced in AD compared with LOS/VLOSLP. Language deficits in LOS/VLOSLP resemble those in AD, and executive function is impaired differentially (but to

a similar degree) in FTD and LOS/VLOSLP. Hence, we might expect to find a pattern of subcortical and cortical atrophy, most pronounced in the frontal and temporal lobes. Reduced processing speed and working memory deficit might also be associated with white matter pathology. Recent systematic review of neurobiological changes in AOS has pointed to similar changes [63]. Specifically, white matter integrity was impaired and grey matter reductions were observable with decreased neuronal integrity. Even though functional networks showed normal architecture, there were alterations in task related activity as well as resting state activity in AOS compared with healthy controls [63].

There has been no research directly linking cognition to neurobiological changes in LOS and VLOSLP. Hence, we will summarize findings concerning the neurobiology of LOS and VLOSLP. Afterwards, we will discuss possible links between findings on the neuropsychology and neurobiology of LOS and VLOSLP. Figure 1 illustrates the main results that will be elaborated on in the following paragraphs. Results were incorporated into this figure only when there was at least one replication in research other than case studies. Dots on a specific brain area represent changes in that particular area, with smaller dots symbolizing that there is only one replication of study results and larger dots meaning that there are multiple replications. It is important to note that most studies discussed used age-matched control groups so as to rule out possible associations with the aging process. There are only a few exceptions with studies including slightly younger [64] or older [65, 66] healthy controls or with studies that do not specify whether the ages are matched, even though older participants are included as healthy controls [67-71].

Volumetric brain changes: atrophy and/or dysgenesis. An increased ventricle to brain ratio (VBR) and larger third ventricles have repeatedly been reported in LOS [67, 68, 72-74], even though the extent of the increase may show differential correlations with the phenomenology of the disease. For instance, Howard et al. [75] report that in late onset

delusional disorder ventricles are more enlarged compared to late onset schizophrenia with hallucinations. An increase in ventricular volume may result from (pathological or age-related) cortical-subcortical atrophy allowing more cerebrospinal fluid (CSF) to fill the intracranial areas. However, less often it is also associated with normal pressure hydrocephaly [76]. Interestingly, Barta et al. [77] noticed that the increase in VBR compared to normal controls is exceeded by that in individuals with Alzheimer's disease. Furthermore, structural brain changes described did not differ fundamentally from the neurodevelopmental changes described in AOS [78].

Many studies have described general patterns of dysgenesis in frontal, parietal, temporal and occipital regions based on neuroimaging research using MRI or CT as well as post-mortem studies [67, 69, 72, 79]. Only one smaller study reported no significant alterations on the MRI's of LOS participants compared to normal controls [80].

Findings with regard to specific patterns of atrophy have been mixed. Preliminary results suggest decreased volumes in the amygdala, entorhinal cortex and (left) hippocampus of LOS and AOS compared with healthy controls [65, 77, 79]. As opposed to the pattern observed in Alzheimer's disease, the anterior superior temporal gyrus volume appeared smaller in LOS than in normal controls [77]. Again, the authors state that this is similar to neural changes in AOS. Coincidently, Rabins et al. [73] found temporal lobe and subcortical atrophy in LOS as opposed to normal controls. Moreover, Howard et al. [81, 82] showed that patients with LOS or VLOSLP who had first-rank symptoms of schizophrenia had less atrophy in the temporal lobe compared to those who did not. Coincidently, media temporal lobe atrophy was significantly smaller in LOS than in Alzheimer's disease [83]. Contrary to observations in LOS, disease duration appeared positively associated with a reduction in the temporal pole in AOS [84]. Additionally, even though the pattern of atrophy described by Rabins et al. [73] was comparable to that found in AOS, the main changes were located in the right hemisphere

whereas AOS is suggested to show more left hemisphere pathology. According to the researcher, the pattern discerned in LOS also differs from changes observed in mood disorders, typically showing more atrophy of superficial cortical sulci [73]. Both AOS and LOS showed smaller grey matter volumes in the right insula, left superior temporal gyrus, and left orbitofrontal gyrus compared to healthy controls [84]. Even though Sachdev and Brodaty [85] did not find abnormalities in the mid-saggital area of the corpus callosum and cerebellum in LOS compared with AOS or normal controls, there was a smaller pontine cross-sectional area in both LOS and AOS. Finally, Barak et al. [72] observed more pronounced cerebellar atrophy in VLOSLP than controls. Still, thalamic volumes in LOS appear greater than those in normal controls and AOS participants [67]. Moreover, Egashira et al. [84] found larger grey matter volumes of the left precuneus in LOS as opposed to healthy controls.

Casanova and Lindzen [86] suggested, based on their post-mortem research, that a significant alteration in the grey matter to white matter ratio in the parahippocampal gyrus of LOS subjects may be explained by a preservation in grey matter and a reduction in white matter. White matter pathology may indeed be an important factor leading to the onset or persistence of psychotic symptoms in late life.

Figure 1. Neurobiological changes in LOS and VLOSLP. OFC: orbitofrontal cortex; IC: insular cortex; AMG: amygdala; STG: superior temporal gyrus; PHG: parahippocampal gyrus; HC: hippocampal cortex

White matter changes and/or (gross) vascular pathology. There is a relatively large consensus concerning the presence of white matter pathology in LOS or VLOSLP [33, 64, 68, 85]. White matter hyperintensities (WMH) and lesions (WML) have been observed in

temporoparietal, frontal and occipital regions [33, 64], in the thalamus [85] and periventricular [53, 85]. There was some inconsistency in findings with regard to subcortical and frontal areas [53, 85, 87], with some studies reporting a relatively preserved structure of the basal ganglia. Su et al. [87], on the other hand, described multiple cortical and subcortical cerebrovascular lesions with WML in bilateral frontal areas. All the subjects in their study also had extensive WML in the anterior and posterior horn, subfrontal areas, thalamus, basal ganglia, internal capsule and pons. These authors propose a neural circuitry hypothesis with regard to the contribution of different brain structures to the onset or maintenance of psychosis in late life.

Still, Howard et al. [88] found no excess in white matter disease in VLOSLP compared to healthy controls. He states that periventricular and deep white matter together with subcortical grey matter hyperintensities are significantly correlated with increasing age and as such may not be considered disease specific. Concurrently, Rivkin et al. [89] and Symonds et al. [66] found that LOS, AOS and healthy controls show comparable white matter pathology. Hence, according to these authors, white matter pathology may only be a contributing factor to late onset psychosis in those individuals more prone to develop schizophrenia.

Connectivity and functionality of different brain areas. White matter disease or other vascular pathology may impede connectivity between different brain regions, which affects functionality of several different brain areas organized into neural networks. Only two studies were conducted that looked into brain connectivity in VLOSLP or LOS using diffusion tensor imaging (DTI) [90, 91]. The first of these studies surprisingly showed no significant differences in fractional anisotropy, mean diffusivity or the orientationally averaged measure of bulk diffusivity between VLOSLP and healthy controls [90]. However, Chen et al. [91] found a significant reduction in fractional anisotropy of the left parietal lobe and the right posterior cingulum in 20 LOS subjects compared to 17 age matched healthy controls, which

suggested that abnormalities in white matter integrity contributed to the pathophysiology of LOS. Still, there were no significant correlations between (the intensity of) psychotic symptoms and fractional anisotropy values, indicating the absence of a dose-effect relationship, which leads the authors to question a causal relationship between reduced white matter integrity and late onset psychosis.

Several studies looked into brain function and its association with late onset psychosis using EEG, ERP, positron emission tomography (PET) and single-photon emission computed tomography (SPECT). LOS subjects show a generalized slowing or a diffuse sharp and slow wave complex in their EEG [92-95], which points to changes in brain metabolism. These could only partially be explained by neuroleptic drug use. Additionally, Olichney et al. [96] found that AOS and not LOS subjects had significantly smaller auditory oddball P300 amplitudes than a healthy control group. They speculated that P300 abnormalities may be a marker for a disease subtype with early onset and more severe information processing deficits. An ERP study by the same research group showed that the mean amplitude in the early portion of the N400, an ERP sensitive to semantic congruity, was reduced in LOS compared with normal controls. This reduction was somewhat sustained in the (older) AOS group. The LOS group did not show delayed N1 and P2 components however, which suggests that the findings were not the result of generalized sensory-perceptual slowing but rather the consequence of abnormal semantic network organization [97].

SPECT studies showed significant differences in regional cerebral blood flow in LOS compared to AOS and healthy controls [37, 68, 98], mainly focused on the frontal and temporal regions bilaterally. In a limited number of cases there was also reduced blood flow in the basal ganglia [68]. There was a lower left to right hemisphere blood flow ratio. Left temporal perfusion was greater in AOS than LOS and not different from controls [37]. Hence, left temporal perfusion was the most discriminating between LOS and normal controls in this

single study. Notably, the study had two controls groups, one age-matched for LOS and another group that was age-matched for AOS. A recent SPECT study compared LOS (n=19), AOS (n=44) and normal controls (n=37), and found reduced regional cerebral blood flow (rCBF) bilaterally in the postcentral gyrus in LOS, whereas AOS showed reduced rCBF precentral and in the inferior frontal gyri [98]. The authors state that there is a significantly differing pattern of brain perfusion in AOS and LOS. In another study, Howard et al. [99] showed no increase in D2-receptor binding in 6 VLOSLP subjects compared to healthy controls. There are several factors that may have caused these discrepancies in study results. One factor may be participant selection criteria. Moreover, functional imaging may reflect temporary changes in brain metabolism. For instance, Van Poeck et al. [100] noticed hypometabolism in the frontal, posterior temporal and bilateral parietal cortex of a 74 year old woman with late onset psychosis, suggestive of Alzheimer's disease. However, during follow-up the cognitive status improved greatly, parietal metabolism increased and a Pittsburgh compound B PET (PIB PET) was negative. Hence, the authors emphasize the importance of cautious interpretation of metabolic changes in VLOSLP.

Neurodegenerative pathology. Five post-mortem studies describe the microstructural changes in LOS compared to AOS and normal controls. First, Casanova et al. [70] observed tau positive glial tangles but no or very little amyloid deposit (typical of Alzheimer's disease), in LOS. Coincidently, Bozikas et al. [101] found comparable neurofibrillary tangle densities in the CA1 of the hippocampus, the entorhinal cortex, and the inferior temporal cortex in AOS, LOS and normal controls, further supporting the hypothesis that LOS is not etiopathologically related to Alzheimer's disease. Additionally, Casanova [71] described restricted limbic tauopathy with little amyloid deposition and preservation of pyramidal cell numbers in the hippocampus of individuals with LOS. He again distinguishes these neuropathologic changes from the alterations associated with Alzheimer's disease, suggesting

that there is a more restricted nature of degenerative changes. In 2003 Casanova and Lindzen found neuritic changes, the preservation of pyramidal cell numbers and diminution of parahippocampal white matter in LOS [86]. These could best be explained, according to the authors, as a dying back neuropathy. Finally, Nagao et al. [102] studied the brains of LOS and VLOSLP subjects and found Lewy body pathology in 26.1%, corticobasal degeneration (CBD) in 4.3% and argyrophilic grain disease (AGD) in 21.7%. Contrary to findings in neuropsychological research, there was no case of pure Alzheimer's disease. Interestingly, this finding suggests that the differential diagnosis of LBD, CBD and AGD versus LOS/VLOSLP may be more challenging than that of AD versus LOS/VLOSLP. This may also suggest that Lewy Body, CBD and AGD pathology may not manifest itself fully before the decease of the participants and hence it may be mistaken for LOS or VLOSLP.

Limitations

There are several limitations to the current review, mainly related to the lack of generalizability of findings. Whereas studies have mostly matched participant groups or statistically controlled for age, education and gender, they do not consistently describe or account for disease duration, cardiovascular risk factors and use of medication. Furthermore, selection criteria varied with respect to clinical participant groups clouding possible differences that may exist between organic or functional psychosis, neurodegenerative disease or 'static' encephalopathy. The international expert consensus has already provided possibilities for increasing uniformity in participant selection in future research [2]. However, the diagnostic categories of LOS and VLOSLP, even though they have been a focus of research the past decade, are usually not separately studied thus masking possible differences between these age groups (see Table 3). Only one study compared LOS and VLOSLP directly [9]. Ideally, a comparison of cognitive function in schizophrenia with different ages at onset

would also involve a discussion of studies independently conducted on each of these disorders. Still, we have only included studies on LOS and VLOSLP and not research focusing solely on the neuropsychology and neurobiology of AOS as this is a very extensive literature and it has recently been discussed in depth by several authors [39, 43-45, 103, 104]. Hence, we used recent meta-analyses to complement the study results of research directly comparing LOS, VLOSLP and AOS with regard to specific cognitive domains. Thirdly, samples were often relatively small. Therefore, caution is required when interpreting study results. For instance, replicated differences might be attributed to multiple testing. On the other hand, a lack of differences in some domains such as social cognition may be due to a lack of power. Also, there is often a cross-sectional study design when extensive neuropsychological evaluation is completed, as opposed to basic screening, whereas a longitudinal design might enable the early detection and follow-up of cognitive deficits in order to determine which cognitive profiles predict a conversion to dementia. Moreover, at present there is still little consensus concerning the use of assessment instruments or imaging techniques. Finally, instead of a meta-analysis, which requires more uniformity in the use of participant criteria and assessment instruments, we have conducted a systematic review. This review strategy may be more prone to interpretation biases. We have tried to avoid this by using a systematic search strategy and a fixed framework for summarizing study results.

Conclusions

Psychosis in late life is a complex and diagnostically challenging symptom. It is often accompanied by cognitive dysfunction which may arise in the context of (neurodegenerative) brain disease or as part of a non-progressive or ‘static encephalopathy’ with a (more) functional nature.

The current review provides some guidelines to aid the differential diagnosis in elderly clients (see Table 4) and understand cognitive deficits in LOS and VLOSLP from a neurobiological perspective. First, older adults with a first incidence of psychosis in the absence of a delirium, mood disorder or neurodegenerative condition might exhibit a mildly progressive executive dysfunction and difficulties in sustaining attention or reduced information processing speed. In general, the reduction in executive function is less pronounced in late onset psychosis compared to AOS. However, VLOSLP subjects showed relatively more impairment on vigilance than LOS subjects, whereas AOS individuals showed intermediate performances. General cognitive abilities and intellectual function show a decrease from average premorbid intelligence to impaired intellectual and general cognitive functioning in LOS and VLOSLP. This coincides with findings in AOS. Reduced processing speed, executive dysfunction and intellectual deterioration all have been linked to ventricular enlargement in adult schizophrenic women. There was no such association in men [105], which is interesting in light of the female preponderance in VLOSLP and LOS. As would be expected, ventricular enlargement and generalized atrophy have rather consistently been observed in studies reporting on brain changes in LOS and VLOSLP. Furthermore, a larger cerebellum is associated with higher IQ in normal controls and affected adult schizophrenic women, but this association is again disrupted in men [105]. This coincides with the finding of cerebellar atrophy in LOS and VLOSLP and the speculated intellectual deterioration. White matter changes may further add to the difficulties in these cognitive domains, but may not be specific to disease onset as they are not consistently associated with psychosis. Some authors suggest that white matter pathology and other vascular brain damage may only precipitate the onset of psychosis in individuals who are prone to develop schizophrenia [88]. In line with this finding which suggests that there are subtypes of LOS and VLOSLP mainly characterized by neurological or rather psychosocial vulnerability, LOS/VLOSLP subjects

sometimes exhibit a generalized cognitive impairment alongside neurological symptoms, though in half of all cases it is characterized by first-rank schizophrenia symptoms and generalized cognitive dysfunction appears absent [28].

Several brain abnormalities have been described in LOS and VLOSLP in areas that are especially involved in executive function and social cognition [106, 107], cognitive domains which are found to be related in late life, suggesting that non-pathological aging may interfere negatively with social cognition through its impact on executive dysfunction [108]. Specifically, the superior temporal gyrus, the orbitofrontal cortex, subcortical structures such as the amygdala, right insula and the cerebellum are affected. However, sociocognition appeared to show only discrete impairment in LOS and VLOSLP, which does not coincide with the general impairment often reported in AOS [11], associated with a neural network involving the prefrontal cortex and amygdala [107]. Hence, researchers have suggested that a relatively spared social cognitive functioning may be a protective factor modulating the age at onset of psychotic symptoms [35]. Moreover, although executive and social cognitive dysfunction often co-occur due to overlapping neural correlates, double dissociations have been described and thus might also exist in LOS/VLOSLP [107]. Still, in LOS and VLOSLP neurobiological (structural and functional) changes have been found in the frontostriatal pathways as well as the amygdala specifically which usually relate to deficits in emotion generation, perception and regulation as well as theory of mind. Also, from a theoretical point of view, an intact social cognitive function in LOS and VLOSLP seems counterintuitive [109]. Coltheart [109] proposes a two factor theory as a neuropsychological basis of the onset and persistence of delusions. A first factor is concerned with the content of delusions, whereas a second factor is related to the persistence of a belief in spite of empirical evidence to the contrary. As paranoid and partition delusions are a hallmark of VLOSLP, based on theoretical models of the neuropsychology of delusions, we would expect two main types of

impairment. The first impairment would be an impaired sociocognition, characterized by so called ‘hypermentalization’ (over-attributing negative intentions to others), which facilitates wrong believes with regard to other people’s intentions, also causing subjects with LOS and VLOSLP to feel threatened. A second impairment is related to the inability to re-evaluate hypotheses once they have been installed through inefficient processing of (sociocognitive) information, causing a wrong inference to maintain rather than be corrected when someone is confronted with reasonable arguments. This second factor is related to deficits in the right dorsolateral prefrontal cortex. Hence, the current findings suggesting preserved sociocognition clearly need replication in larger samples and may not necessarily be confirmed.

Memory and language impairment in LOS/VLOSLP can be related to clearly documented changes in the temporal lobe, including the superior temporal gyrus, the entorhinal cortex, the parahippocampal gyrus and the hippocampal formation. First episode psychosis at a younger age is also specifically associated with reduced processing speed and verbal learning according to a recent meta-analysis [40]. These impairments are related to prefrontal (PFC) and temporal lobe (MTL) volume reductions or altered glucose metabolism and connectivity.

Finally, perception and visuoconstruction might be problematic in LOS and VLOSLP, although impairment has not been consistently reported and may be the result of concurrent executive dysfunction or semantic deficits.

In summary, the current results seem compatible with a frontal, temporal and subcortical brain involvement in LOS and VLOSLP. Frontostriatal circuits have indeed been targeted by some authors as possible neurobiological correlates of cognitive and psychological symptoms in LOS and VLOSLP [37].

Frontotemporal involvement as well as subcortical neurobiological structural and/or functional changes might be indicative of a neurodegenerative illness. Still, the mildly

progressive nature of deficits contrasts with the more pronounced decline in neurodegenerative conditions such as AD or FTD, known to have predominantly temporal and frontal neuroanatomical correlates. Coincidently, atrophy in the medial temporal lobe is less pronounced in LOS/VLOSLP than that in AD and unrelated to disease duration. Moreover, individuals with more first rank symptoms of schizophrenia had less atrophy in the temporal lobe compared to those who did not. As opposed to AD, the anterior superior temporal gyrus in LOS and VLOSLP seems smaller than that in normal controls. In AD there is often a steady decline, and already at baseline assessments there are apparent dissimilarities in consolidation capacities compared with LOS and VLOSLP. Learning deficits usually exceed consolidation difficulties in LOS/VLOSLP compared to AD, and it is unclear whether executive dysfunction moderates learning impairment, for instance because of the lack of efficient processing/learning strategies or disinhibition during free recall [110]. VLOSLP/LOS might show more intrusions in delayed recall, whereas AD patients simply do not recall the correct items. This is compatible with the hypothesis of a source monitoring deficit in psychosis, as proposed in earlier research on (AO)S [111, 112]. Coincidently, executive dysfunction seems less pronounced in AD than in LOS/VLOSLP. In FTD the executive dysfunction slightly differs from that observed in LOS and VLOSLP. Specifically, verbal fluency, abstraction and cognitive flexibility, as opposed to working memory, may prove stronger in LOS than in FTD. The absence of a neurodegenerative condition in at least part of the individuals diagnosed with LOS or VLOSLP is further suggested through the lack of clear neuropathological changes reported in postmortem research.

Importantly, though, an overlap in certain clinical (or cognitive) characteristics as well as neurobiological changes between LOS/VLOSLP and neurodegenerative conditions with coinciding psychotic symptoms is not surprising as there may be a similar biological basis contributing to onset and maintenance of psychotic symptoms transdiagnostically.

Specifically, in LOS and/or VLOSLP we may observe a stress-related accelerated brain aging. Indeed, early and adults life stress have been associated with LOS/VLOSLP as well as (pre)frontal and temporal atrophy, also extending to the limbic structures such as the hippocampus and amygdala [113-115]. These alterations may, however, not be as pronounced as those in neurodegeneration. The additional neurobiological changes occurring in late life, combined with a psychosocial vulnerability and a certain degree of genetic predisposition, may trigger the onset of late life psychosis. These different factors may, however, have a differential impact on the onset of psychosis in late life within several individuals, causing the group of individuals with LOS and especially VLOSLP to show heterogeneous clinical characteristics. Still, for any individual a combination of genetic, psychosocial and (age-related) neurobiological factors is hypothesized to lead to a situation where individuals supersede a threshold for the development of psychotic symptoms only later in life as genetic vulnerability seems smaller compared to early or adult onset schizophrenia, which also leads to better occupational and marital histories [2].

However, it is clear that many cognitive domains have insufficiently been explored and study results have unsatisfactorily been replicated in large participant groups that yield enough power to draw firm conclusions. Studies directly linking neuropsychological measures to neurobiological variables may allow further clarification of the biological mechanisms contributing to the onset of psychosis in late life. Still, we suspect that biological factors may only partly enlighten the etiopathology of LOS or VLOSLP. To completely comprehend the onset of psychosis in adult as well as late life, psychosocial factors (personality, life events, social support, …) need to be taken into account.

Surprisingly, also, studies on FTD and AD versus LOS or VLOSLP exist but there is no research that addresses differential diagnosis with respect to LBD, even though there is an important overlap in clinical presentation. Specifically, delusions and visual hallucinations

may occur in both conditions. Moreover, LBD is often characterized by executive and perceptual dysfunction. Additionally, neuropathological research has demonstrated that misdiagnosis of VLOSLP and LBD patients is not uncommon. Future research on differential diagnosis between LBD and LOS/VLOSLP is needed as clinicians may exceedingly be confronted with both illnesses in an aging world population.

Taking into account the limitations described earlier, there is also an urgent need for research with a longitudinal design, using standardized test instruments in combination with strict selection criteria for participant groups based on an international consensus [2]. Furthermore, studies that aim to characterize the cognitive profile of LOS/VLOSLP and compare this to neurodegenerative conditions might benefit from the inclusion of imaging data to which specific cognitive deficits may be correlated. Coincidently, further exploration of the existence of different (cognitive) subtypes of LOS/VLOSLP may also be interesting as well as their neurobiological correlates. Different subtypes of LOS and VLOSLP may be precursors of differing neurodegenerative conditions or 'purely' functional psychosis. Admittedly, a purely functional psychosis in late life may not exist as non-pathological brain ageing – combined with psychosocial stressors – might also trigger an earlier existent vulnerability in VLOSLP and LOS subjects.

Finally, cognitive remediation in this population has not been studied yet, and may prove valuable, especially since (social) cognitive dysfunction was shown to be an important mediator of functional outcome in AOS [104].

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